Catalytic Enantioselective Tosylation of Meso-Alcohols with an Amino-Acid-Based Small Molecule

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CATALYTIC ENANTIOSELECTIVE TOSYLATION OF *MESO*-ALCOHOLS WITH AN AMINO-ACID-BASED SMALL MOLECULE

a thesis

by

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Catalytic Enantioselective Tosylation of *meso*-Alcohols with an Amino-acid-based Small Molecule

Fengqi Wen

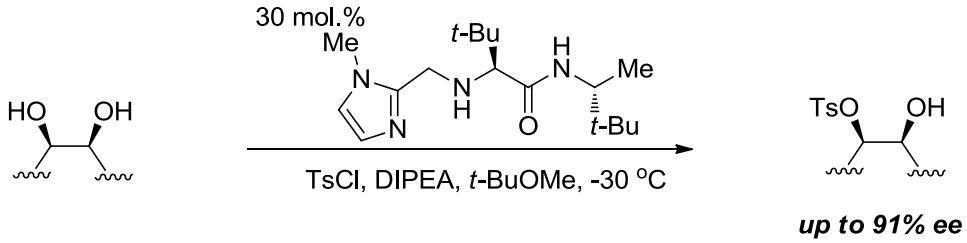
Thesis Advisor: Professor Marc L. Snapper

ABSTRACT

Chapter 1 Review of methodology developments in the area of selective tosylation of alcohols.

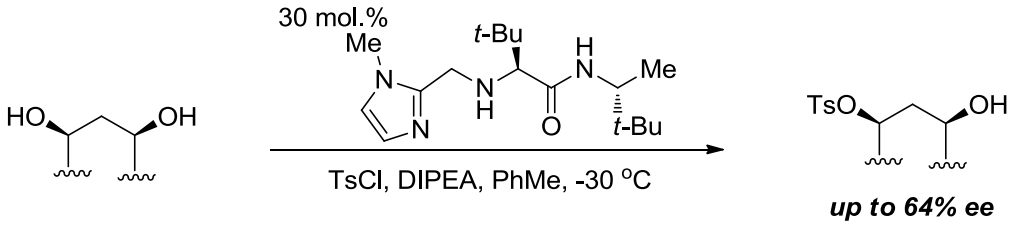
Chapter 2 Development of a catalytic enantioselective tosylation of alcohols with an amino-acid-based organocatalyst.

***meso*-1,2-diols**



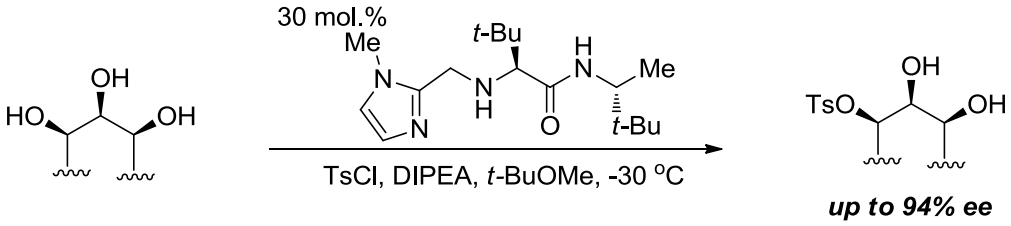
up to 91% ee

***meso*-1,3-diols**



up to 64% ee

***meso*-1,2,3-triols**



up to 94% ee

TABLE OF CONTENTS

CHAPTER 1 REVIEW OF METHODOLOGY DEVELOPMENTS OF SELECTIVE TOSYLATION OF ALCOHOLS 1

1.1 Introduction and Background 1

1.2 Mono/Bis selective Tosylation of Symmetric Diols 1

1.3 Chemoselective Tosylation of Alcohols 3

1.4 Enantioselective Tosylation of *meso*-1,2-Diols 4

1.5 Enantioselective Sulfonylation of meso-1,3-diols 5

1.6 Kinetic Resolution of *rac*-Alcohols Through Tosylation 8

1.7 Synthetic Application of Enantioselective Tosylation 9

1.8 Conclusion and Outlook 12

CHAPTER 2 DEVELOPMENT OF A CATALYTIC ENANTIOSELCETIVE TOSYLATION OF ALCOHOLS WITH AN AMINO-ACID-BASED ORGANOCATALYST 13

2.1 Introduction and Background 13

2.2 Initial Exploration of Enantioselective Tosylation 15

2.3 Reaction Condition Optimization 17

Catalyst Loading

Solvent Effect

Kinetic Resolution of rac-mono-Tosylate

Concentration and Temperature Evaluation

Base Optimization

Sulfonylation Reagent Study

Conclusion of Condition Modifications

2.4 Modification of the Catalyst 28

Modification of Lewis Base
Modification of the Amino Acid
Modification of Amide
Diamino Acid Based Modifications
Other Modifications
2.5 Substrate Scope
meso-1,2-diols
meso-1,3-diols
cis-meso-1,2,3-Triols
2.6 Summary 42
2.7 Experimental and Supporting Information 43
General Information 43
Characterization Data 59

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Finally, I want to thank my family for their endless encouragement and love. They have been my strength and support during my entire life.

Chapter 1

Review of Methodology Developments in the Area of Selective Tosylation of Alcohols

1.1 Introduction and Background

Sulfonylation is well recognized as a fundamental transformation in organic synthesis.[1] Since the sulfonyl ether group is a better leaving group than the hydroxyl group, sulfonylation is commonly used to convert alcohols into substrates that can undergo nucleophilic substitutions. Among sulfonylations, tosylation is one of the most used transformations. Tosylation can be carried out with tosyl anhydride and *p*-toluenesulfonic acid, however, tosyl chloride (TsCl) is the most widely used tosylation reagent due to its high reactivity and mild reaction conditions.[2] Generally, tosylation of alcohols is carried out with TsCl in the presence of a base, such as pyridine or triethylamine. The sulfonate products of alcohols can readily undergo nucleophilic substitution. This process allows for the transformation of a molecule with a C-O bond into a series of valuable molecules containing new C-C, C-N, and C-O bonds with inverted stereochemistry in high enantiomeric purity for some secondary systems. Therefore, enantioselective sulfonylation can be a very powerful synthetic tool in organic chemistry.

1.2 Mono/Bis selective Tosylation of Symmetric Diols

The selective tosylation of primary alcohols over secondary and tertiary alcohols can be well controlled due to their distinct steric and electronic differences. However, in the case of a diol, if both of the hydroxyl are primary/secondary, the bis-tosylate can be the dominant

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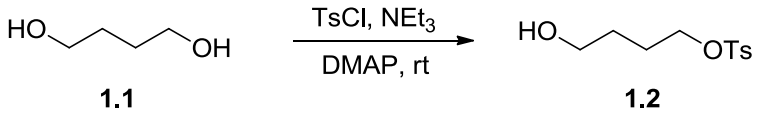
[1] (a) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, **1999**. (b) Smith, M. B. and March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley, New York, **2001**, pp. 576.

[2] Kabalka, G.W.; Varma, M.; Varma, R.S.; Srivastava, P.C.; Knapp, F.F., Jr. *J. Org. Chem.* **1986**, *51*, 2386-2388.

product of tosylation.[3]

In 1994, Ahlberg and Wu reported a selective mono-tosylation route to synthesize 4-hydroxybutyl *p*-toluenesulfonate from 1,4-butanediol (Scheme 1.1).[4] They found that it was critical to not use any solvent, but to instead use an excess amount of triethylamine. In the presence of solvent, the bis-tosylate was the major product, even while using excess diol. This probably originates from the better solubility of mono-tosylate than diol.

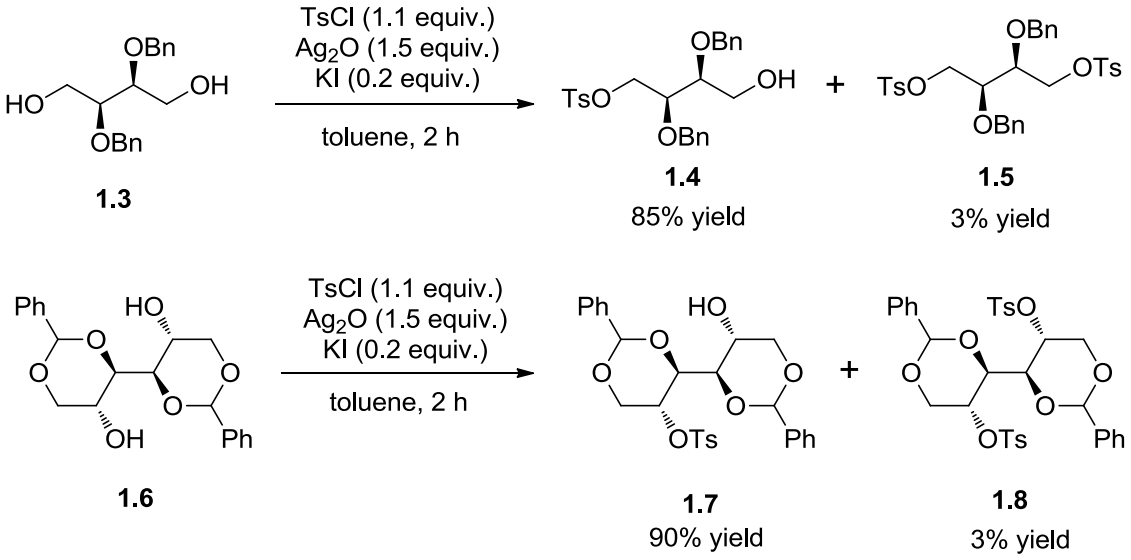
Scheme 1.1. Ahlberg and Wu's Selective mono-Tosylation of 1,4-Butanediol



1.1 **1.2**

Later, Bouzide and co-workers discovered a route for the selective mono-tosylation of symmetric diols in the presence of silver (I) oxide and a catalytic amount of KI (Scheme 1.2).[5]

Scheme 1.2. Silver (I) Oxide Mediated Selective mono-Tosylation of Symmetric Diols



1.3 **1.4** 85% yield **1.5** 3% yield

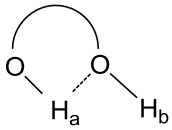
1.6 **1.7** 90% yield **1.8** 3% yield

[3] (a) O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1992**, *57*, 4775-4777; (b) Katritzky, A. R.; Zhang, G.; Wu, I. *Synth. Commun*. **1994**, *24*, 205-216.
[4] Wu, Y.; Ahlberg, P. *J. Org. Chem.* **1994**, *59*, 5076-5077.
[5] Bouzide, A.; Sauve, G. *Org. Lett.* **2002**, *4*, 2329-2332.

In their substrate scope study, both primary and secondary symmetric diols had very good mono/bis selectivity. For example, primary diol **1.3** generated 85% mono-toylate **1.4** and 3% bis-tosylate **1.5** in the reaction, while, secondary diol **1.6** afforded 90% mono-tosylate **1.7** and 3% bis-tosylate **1.8** under the reaction conditions.

The achievement of the high mono/bis-tosylate ratio is attributed to the internal hydrogen bonding. Hydrogen H_a is less acidic than hydrogen H_b due to its acceptance of electrons from hydrogen bonding (Figure 1).[6] Therefore, hydrogen H_b will be selectively deprotonated by Ag_2O, hence giving the mono-tosylate as the dominant product when a stoichiomeric amount of TsCl is used.

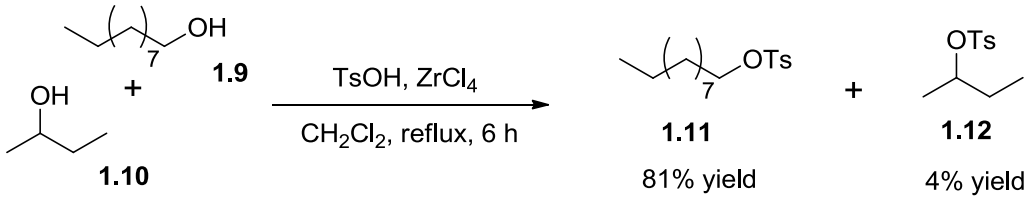
Figure 1.1



1.3 Chemoselective Tosylation of Alcohols

Since primary alcohols are less sterically hindered than secondary alcohols, temperature control can be used to achieve such selectivity; however, low temperature leads to low reactivity or long reaction times. In 2004, Das and coworkers reported using $ZrCl_4$ as an efficient catalyst for the chemoselective tosylation of primary alcohols over secondary alcohols in refluxing CH_2Cl_2 (Scheme 1.3).[7]

Scheme 1.3. $ZrCl_4$ as a Efficient Catalyst for Chemoselective Tosylation



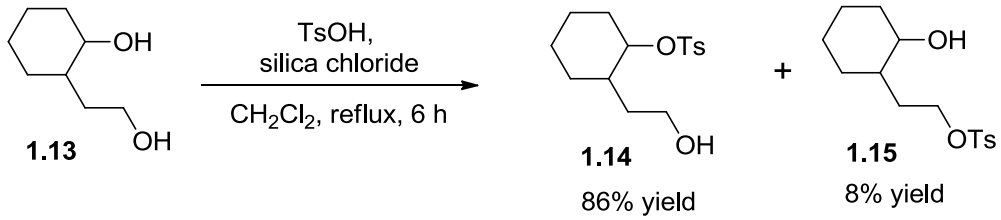
Under the reaction conditions, a 1:1 mixture of primary alcohol **1.9** and secondary alcohol

[6] Busfield, W. K.; Ennis, M. P.; McEwen, I. J. *Spectrochim. Acta*. **1973**, *29A*, 1259-1264.
[7] Das, B.; Reddy, V. S. *Chem. Lett*. **2004**, *33*, 1428-1429.

1.10 led to 81% yield of primary tosylate **1.11** and 4% secondary tosylate **1.12**, which showed high selectivity.

Later in 2004, Das and coworkers developed a direct tosylation with *p*-TsOH using silica chloride, which was prepared from silica gel and thionyl chloride, as a heterogeneous catalyst to chemoselectively tosylate secondary alcohols over primary alcohols.[8] As shown in Scheme 1.4, diol **1.13** consists of both primary and secondary alcohols. Under the catalysis of silica chloride, secondary tosylate **1.14** was afforded in 86% yield, while primary tosylate **1.15** was generated in only 8% yield. These results showed the preference for the tosylation of the secondary alcohol under these reaction conditions.

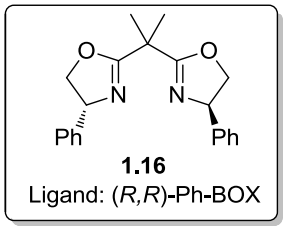
Scheme 1.4. Chemoselective Tosylation Reaction with TsOH



1.4 Enantioselective Tosylation of *meso*-1,2-Diols

In 2007, Onomura, Matsumura and coworkers reported their enantioselective tosylation of *meso*-diols using a copper (II) complex with box ligand **1.16** (Figure 1.2).[9] In the proposed transition state model (Scheme 1.5), a copper (II) ion associates with chiral box ligand **1.16**,[10] and this system recognizes and desymmetrizes *meso*-1,2-diol **1.17** by forming a five-membered ring complex **1.18**. Then TsCl reacts with the complex in the presence of base

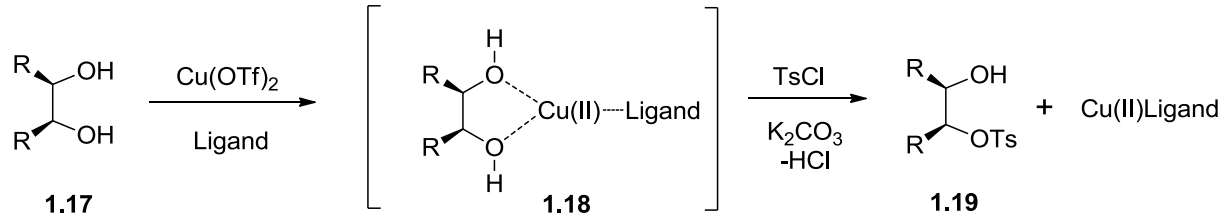
Figure 1.2



[8] Das, B.; Reddy, V. S.; Reddy, M. R. *Tetrahedron Lett.* **2004**, *45*, 6717-6719.
[9] Demizu, Y.; Matsumoto, K.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2007**, *48*, 7605-7609.
[10] Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052-2053.

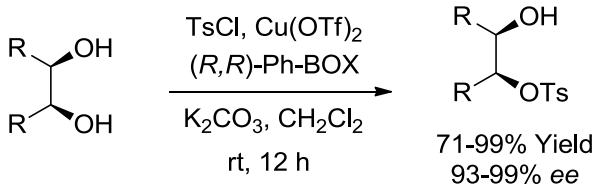
and generates enantioselective product **1.19**.

Scheme 1.5. Enantioselective Tosylation of *meso*-1,2-Diols by a Copper(II) Complex



In their research, a series of *meso*-1,2-diol substrates, including cyclic and acyclic diols were evaluated using this methodology. The yield and enantiomeric excess of the products are moderate to excellent (Scheme 1.6).

Scheme 1.6. Onomura and Matsumura's Enantioselective Tosylation of *meso*-1,2-Diols



Due to the copper catalyzed process having a strong preference for forming a five-membered chelate,[11] which could be derived from 1,2-diols, this methodology is not likely to be applicable to the desymmetrization of *meso*-1,3-diols.[12]

1.5 Enantioselctive Sulfonylation of *meso*-1,3-Diols

An impressive example of enantioselective sulfonylation of *meso*-1,3-diols was published in 2010 by Miller and coworkers. They reported an enantioselective nosylation mediated by a π-methyl histidine-based tetramerictetrapeptide catalyst **1.20** (Figure 1.3).[13]

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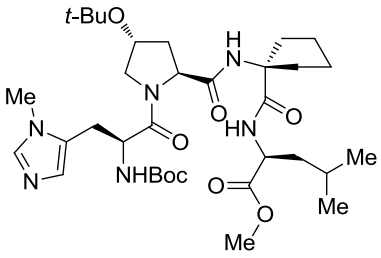
[11] Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13-31.
[12] (a) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887-2902; (b) Geurts, K.; Fletcher, S. P.; Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Pure Appl. Chem.* **2008**, *80*, 1025-103.
[13] Fiori, K. W.; Puchlopek, A. L. A.; Miller, S. J. *Nature Chemistry* **2009**, *1*, 630-634.

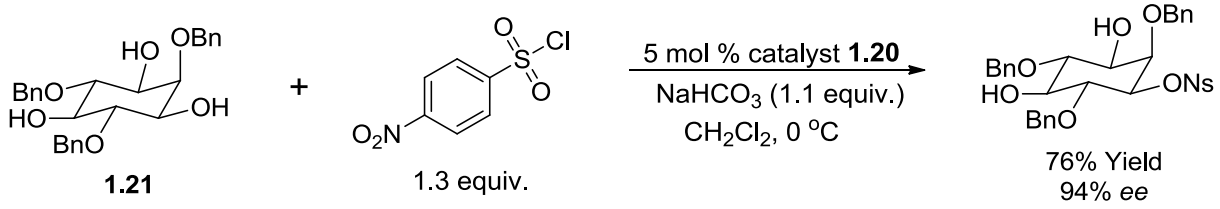
2,4,6-Tribenzyl-*myo*-inositol **1.21** was chosen as the test substrate. In the presence of 1.1 equiv. $NaHCO_3$ as base and 5 mol % catalyst **1.20**, the substrate reacted with 1.3 equiv. *p*-NsCl in CH_2Cl_2 at 0 ℃ for hours, giving 76% yield and 94% enantiomeric excess of the mono-nosylate product (Scheme 1.7). This methodology was applied to a number of *meso*-1,3-diols.

Figure 1.3



1.20
Miller's catalyst

Scheme 1.7. Miller's Enantioselective Nosylation of *meso*-1,3-Diols

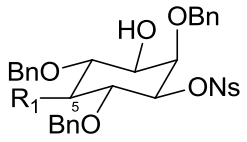


The enantiomeric excess of different mono-nosylate products is found to be substrate dependent. For substrates **1.22**, **1.23**, **1.24** and **1.25**, which only differ by their substituents on carbon 5 of 2,4,6-tribenzyl-*myo*-inositol, the products have moderate yields and high *ee* values (Scheme 1.8). The same is true for substrates **1.26** and **1.27**, whose substituents differ on carbon 2 of 2,4,6-tribenzyl-*myo*-inositol. However, if the *meso*-1,3-diols are *cis*-cyclohexane-1,3-diol **1.28** or acyclic *meso*-1,3-diols **1.29** and **1.30**, the yield of the reaction is low and there is either no or very poor enantioselectivity.

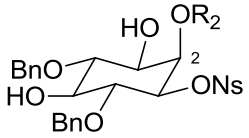
In summary, compound **1.20** is an efficient catalyst in desymmetrizing 2,4,6-protected-*myo*-inositols and its derivatives. The reaction is quite tolerant of modifications at position 5 of

inositol, while some changes at position 2 of inositol will damage the enantioselectivity. Small and simple *meso*-1,3-diols **1.29**, **1.30** and **1.31** fail at being desymmetrized by catalyst **1.20**.

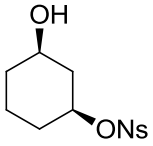
Scheme 1.8. Substrate Scope of Miller's Enantioselective Nosylation of *meso*-1,3-Diols



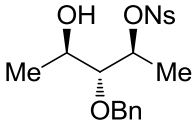
1.22 R_1 = H, 58%, 91% *ee*
1.23 R_1 = O, 76%, 92% *ee*
1.24 R_1 = OTBS, 62%, 91% *ee*
1.25 R_1 = CH_2, 75%, 93% *ee*



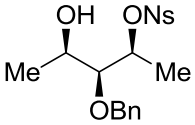
1.26 R_2 = Me, 57%, 76% *ee*
1.21 R_2 = Bn, 76%, 94% *ee*
1.27 R_2 = PMB, 75%, 94% *ee*



1.29
12% Yield
0% *ee*



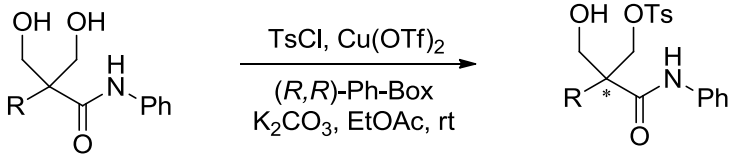
1.30
74% Yield
78% *ee*



1.31
16% Yield
24% *ee*

In 2008, the Matsumura and Onomura group reported another example of enantioselective sulfonylation of *meso*-1,3-diols.[14] They used the (*R*,*R*)-Ph-Box ligand and copper (II) triflate as a catalyst to achieve enantioselective tosylation of 2,2-bis(hydroxymethyl)alkanamides as shown in Scheme 1.9.

Scheme 1.9. Matsumura and Onomura' Enantioselective Tosylation of *meso*-1,3-Diols



1.32 R=H
1.33 R=Me
1.34 R=Et

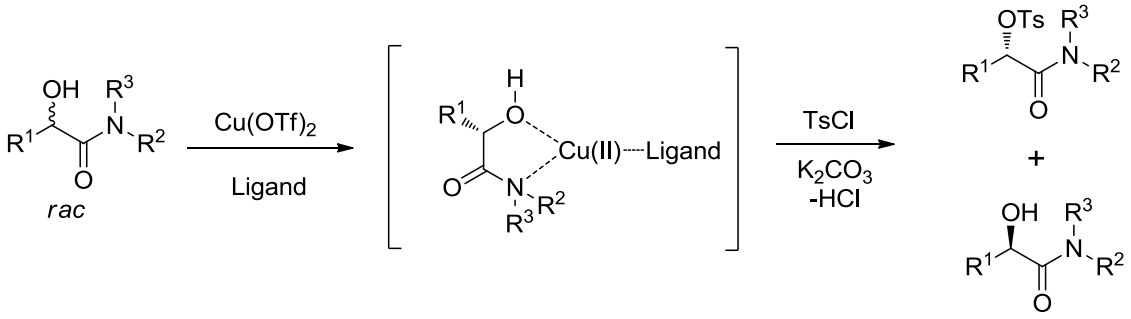
R=H, 89% yield, 85% *ee*
R=Me, 99% yield, 90% *ee*
R=Et, 85% yield, 85% *ee*

[14] Demizu, Y.; Kubo, Y.; Matsumura, Y.; Onomura, O. *Synlett* **2008**, *20*, 433-436.

1.6 Kinetic Resolution of *rac*-Alcohols Through Tosylation

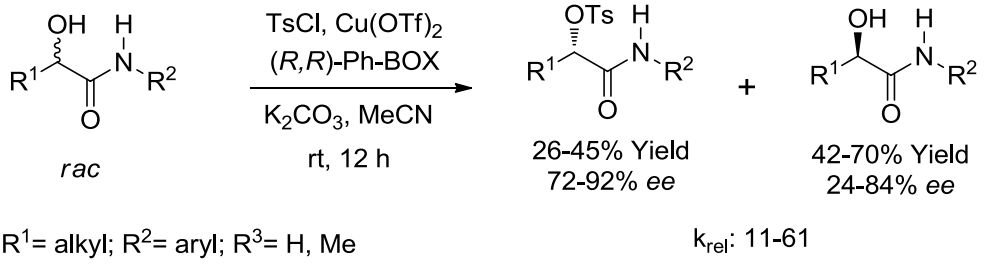
Based on their asymmetric tosylation research, the Matsumura and Onomura group reported asymmetric tosylation of 2-hydroxylalkanamides with the same copper catalyst described above (Scheme 1.10).[15, 16] The amide group in the 2-hydroxylalkanamide plays the same role of the hydroxyl group in the transition state, chelating to copper (II) and forming the five-membered ring intermediate.

Scheme 1.10. Kinetic Resolution of *rac*-2-Hydroxylalkanamides through Tosylation by a Copper(II) Complex



Primary amides as substrates in this kinetic resolution are preferred, and can have k_{rel}'s up to 61. Secondary amides, however, had very poor yields and selectivities, which might be due to the steric bulk of secondary amides. It can block the hydroxyalkanamide from forming the five-membered ring intermediate with the copper catalyst (Scheme 1.11).

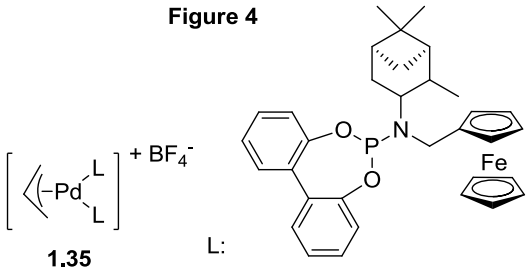
Scheme 1.11. Substrate Scope of Kinetic Resolution of *rac*-2-Hydroxylalkanamides through Tosylation



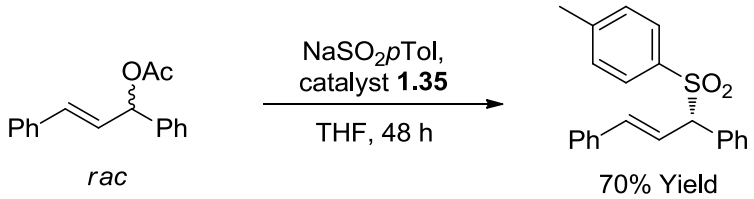
[15] Onomura, O.; Mitsuda, M.; Nguyen, M. T. T.; Demizu, Y. *Tetrahedron Lett.* **2007**, *48*, 9080-9084.
[16] Demizu, Y.; Matsumoto, K.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2007**, *48*, 7605-7609.

In 2005, Gavrilov and co-workers reported an asymmetric allylic sulfinylation of 1,3-diphenylallyl acetate with sodium *p*-toluenesulfinate (Scheme 1.12).[17] The sulfinylation used a palladium catalyst **1.35** with arylamidophosphite and terpenoid complex as the ligand (Figure 4).

Figure 4



Scheme 1.12. Palladium-Catalyzed Enantioselective Sulfinylation



1.7 Synthetic Application of Enantioselective Tosylation

Sulfonylation is commonly used to convert alcohols to their precursors for S_N2 reaction due to its good leaving ability. This process allows conversion of a molecule with a C-O bond into a series of valuable molecules containing new C-C, C-N, and C-O bonds with inverted stereochemistry in high enantiomeric purity. Therefore, enantioselective sulfonylation can be a very powerful synthetic tool in organic chemistry.

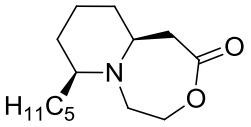
Nitrogen-based nucleophilic substitution

There are a lot of different nitrogen-based nucleophiles, such as azides and amines. Blechert and coworkers have reported a S_N2 reaction between an amine and a tosylate in their synthesis of (+)-Calvine (Figure 5). They reacted ethanolamine **1.36** with tosylate **1.37** in refluxing THF for 6

[17] Zheglov, S. V.; Lyubimov, S. E.; Davankov, V. A.; Gavrilov, K. N. *Russ. J. Coord. Chem.* **2005**, *31*, 834-835.

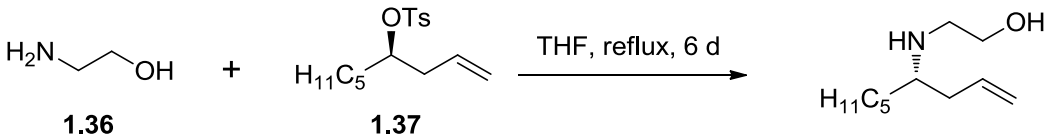
days. Even though they failed to determine the complete inversion of configuration (S_N2 mechanism) directly via chiral HPLC or Mosher derivatives, the enantiopurity of calvine confirmed the complete inversion of configuration of the nucleophilic substitution reaction (Scheme 1.13).[18]

Figure 5



(+)-calvine

Scheme 1.13. Example of Tosylate Undergoing Nucleophilic Substitution with N-Nucleophile

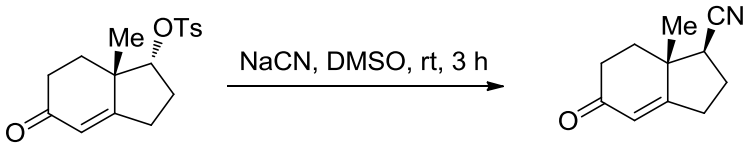


1.36 **1.37** 77%

Carbon-based nucleophilic substitution

Carbon nucleophiles are most likely to be alkyl metal halides, enols/enolates, cyanides and anions of terminal alkynes. These can be employed in various reactions, such as Barbier type reactions and condensation reactions. However, due to the strong basicity of alkyl metal halides, elimination is usually the main reaction. Cyanide is a mild base and strong nucleophile and it can therefore react with tosylates under S_N2 conditions smoothly. One example is given by Deslongchamps and coworkers in their synthetic studies toward highly functionalized 5*β*-lanosterol derivatives (Scheme 1.14).[19]

Scheme 1.14. Example of Tosylate Undergoing Nucleophilic Substitution with C-Nucleophile



86%

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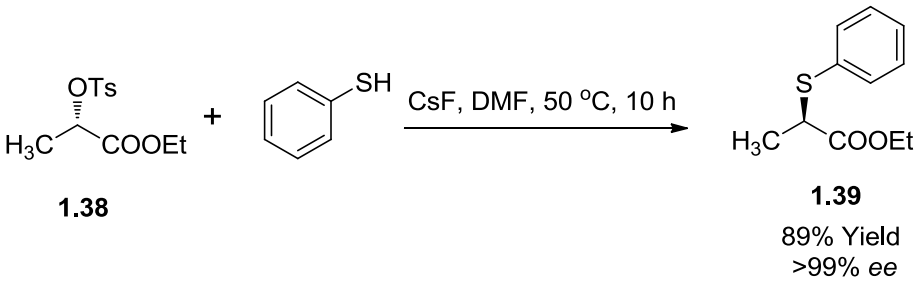
[18] Wülfing, P. D.; Gebauer, J.; Blechert, S. *Synlett.* **2006**, *18*, 487-489.
[19] Ramachandran, S.A.; Kharul, R. K.; Marque, S.; Soucy, P.; Jacques, F.; Chenevert, R.; Deslongchamps, P. *J. Org. Chem*. **2006**, *71*, 6149-6156.

Sulfur-based nucleophilic substitution

Of the sulfur nucleophiles, thiols/thiolate anions and thiolcarboxylic acid anions are used most often. Due to the large size of the sulfur atom, it is very easy to be polarized. This makes it a good nucleophile.

Otera and coworkers have reported examples of CsF promoted inversion of secondary mesylates and tosylates.[20] When tosylate **1.38** and thiophenol are heated to 50 ℃ in DMF for 10 h in the presence of CsF, they give product **1.39** with complete inversion of configuration.

Scheme 1.14. Example of Tosylate Undergoing Nucleophilic Substitution with S-Nucleophile



1.38

1.39

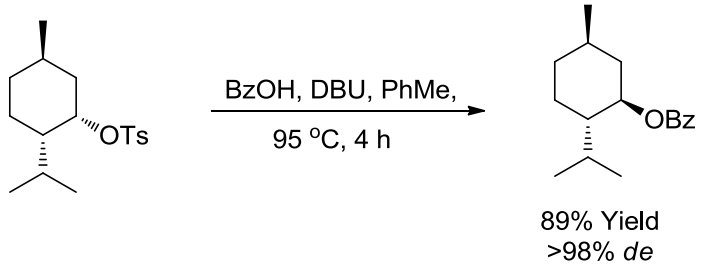
89% Yield

>99% *ee*

Oxygen-based nucleophilic substitution

Examples of oxygen nucleophiles are hydroxide, alcohols/alkoxides, and carboxylate anions. Shi and coworkers carried out the following transformation with inversion of stereochemistry of

Scheme 1.15. Example of Tosylate Undergoing Nucleophilic Substitution with O-nucleophile



89% Yield

>98% *de*

[20] Otera, J.; Nakazawa, K.; Sekoguchi, K.; Orita, A. *Tetrahedron*, **1997**, *53*, 13633-13640.

a secondary chiral tosylate, using a benzyloxy group to replace the tosyloxy group with more than 98% inversion of configuration (Scheme 1.15).[21]

1.8 Conclusion and Outlook

Due to its extensive application in synthetic chemistry, tosylation has been thoroughly studied. However, few enantioselective tosylations of alcohols have been reported. Even though there is some excellent work done by Onomura group on enantioselective tosylation of *meso*-1,2-diols and Miller group on enantioselective nosylation of 2,4,6-tribenzyl-*myo*-inositol derivatives, both methodologies have strict substrate restrictions. A more general, reliable catalytic enantioselective tosylation of alcohols still needs to be developed.

[21] Shi, X. X.; Shen, C. L.; Yao, J. Z.; Nie, L. D.; Quan, N. *Tetrahedron*, **2010**, *66*, 277-284.

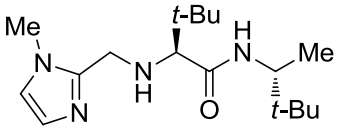
Chapter 2

Development of a Catalytic Enantioselective Tosylation of Alcohols with an Amino-acid-based Organocatalyst

2.1 Introduction and Background

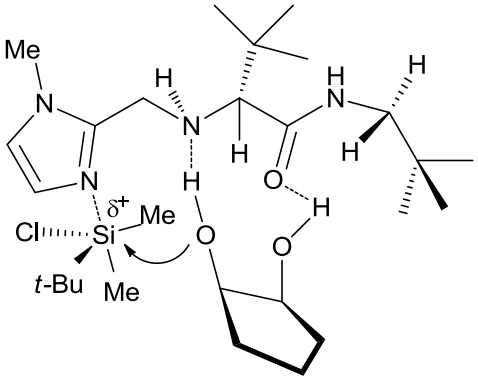
Over the several few years, the Snapper and Amir groups has developed several catalytic transformations using amino-acid-based catalysts. Particularly, the first catalytic enantioselective silylation for desymmetrization of *meso*-diols has been reported.[22, 23, 24] A highly selective single-amino-acid-derived catalyst **2.1** was designed and synthesized (Figure 6). Catalyst **2.1** can interact with diols through hydrogen bonding to desymmetrize them; then the Lewis base moiety, *N*-methylimidazole, can catalyze the silylation of the nearest hydroxyl group (Scheme 2.1).

Figure 6



2.1

Scheme 2.1. Proposed Transition State Model for Catalytic Enantioselective Silylation of Diol



Dr. Yu Zhao and Dr. Jason Rodrigo developed this method of enantioselective silylation of

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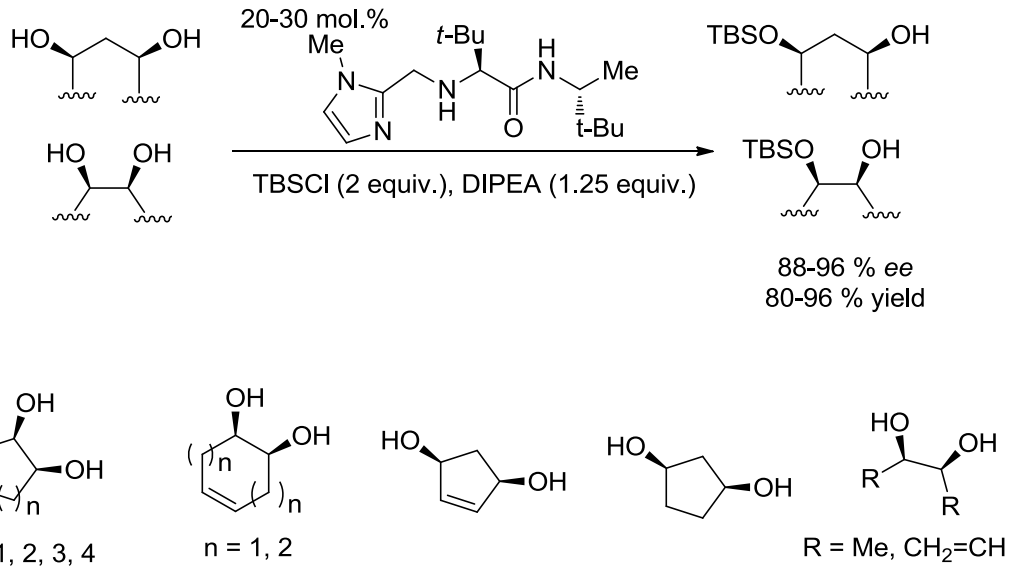
[22] Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67-70.
[23] Zhao, Y.; Mitra, A. W.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 8471.
[24] You, Z.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem. Int. Ed.* **2009**, *48*, 547.

meso-1,2-diols. This methodology can be applied successfully to a series of *meso*-1,3-diols, including cyclic *meso*-1,2-diols, cyclic *meso*-1,3-diols and some acyclic *meso*-1,2-diols (Scheme 2.2).

Scheme 2.2. Substrate Scope of Catalytic Enantioselective Silylation of *meso*-diols



The mechanism of enantioselective silylation of diols was thought to involve hydrogen bonding of the diol to the backbone of the catalyst. The diol approaches the catalyst in one direction so as to minimize steric hindrance; hence, the two hydroxyl groups are desymmetrized. The *N*-methylimidazole moiety, which is a Lewis basic site, can activate the silyl chloride through a hypervalent complex involving three-center four-electron (3c-4e) bonding.[25, 26, 27] Then, the hydroxyl group, which is nearest to the activated silyl hypervalent complex gets silylated selectively. This method can provide up to 96% enantiomeric excess purity of the mono-silylated products with good yields.

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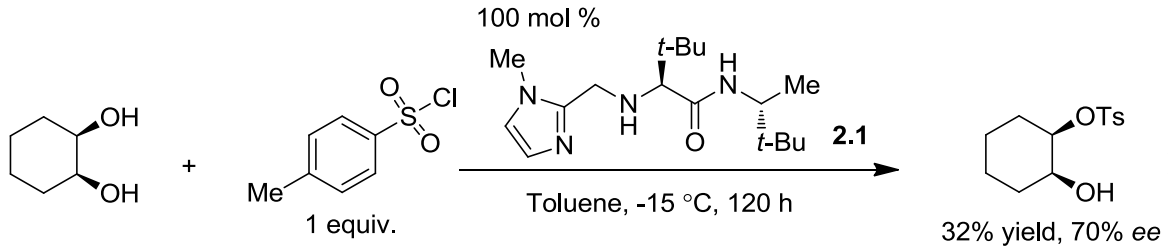
[25] Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed*. **2008**, *47*, 1560-1638.
[26] Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc*. **2003**, *125*, 7800-7801.
[27] Denmark, S. E.; Heemstra, J. R. Jr. *Org. Lett*. **2003**, *5*, 2303-2306.

2.2 Initial Exploration of Enantioselective Tosylation

Since catalyst **2.1** can desymmetrize *meso*-1,2-diols and *meso*-1,3-diols through silylation, it has the potential to be applied to other enantioselective functionalizations of *meso*-diols or *meso*-triols. The Lewis base activation principle can also be applied to other enantioselective functionalizations of *meso*-alcohols. *N*-methylimidazole is a good activating ligand for silicon,[28] similarly, there are examples of using pyridine or triphenylphosphine oxide to activate sulfonyl chloride.[29] This implies that it is possible to use Lewis bases to activate a sulfonyl chloride and promote sulfonylation.

Dr. Zhen You from the Snapper group first applied this principle towards enantioselective sulfonylation. Due to its vast applications in synthetic chemistry, low price, and convenience of purification, tosyl chloride was chosen as the sulfonylation reagent. The test reaction Dr. You ran used stoichimetric amount of catalyst **2.1**, *meso*-1, 2-cyclohexanediol and 1 equiv. TsCl in toluene at -15 ℃ for 5 days (Eq. 1).



Eq. 1

The preliminary result showed that it is possible to use the amino-acid-based Lewis basic catalyst to achieve enantioselective tosylation. It's not surprising that catalyst **2.1** could desymmetrize the diol; moreover, the *N*-methylimidazole moiety did activate the TsCl, which was supported by further background exploration. Since the catalyst has a secondary amine

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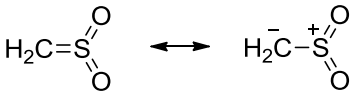
[28] Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc*. **2003**, *125*, 7825-7827.
[29] Signore, G.; Malanga, C.; Menicagli, R. *Tetrahedron*. **2008**, *130*, 11218-11223.

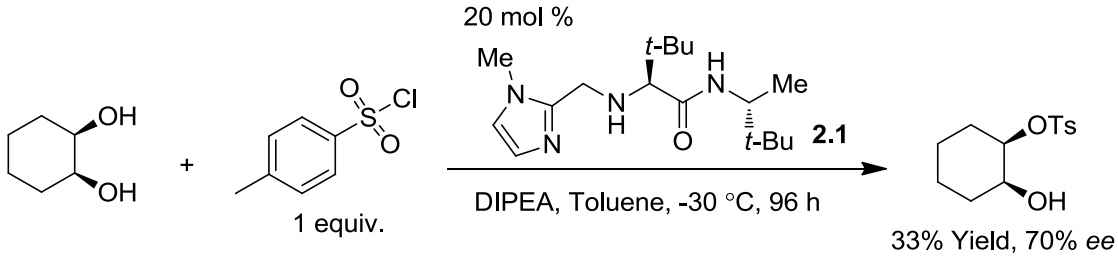
moiety which can function as the base to deprotonate the intermediate (tosylalkyloxonium), a background reaction with TsCl and *meso*-diol in the presence of Et_3N was set up in toluene at -15 ℃. The result of this background reaction showed trace conversion, which supports that *N*-methylimidazole catalyzes the tosylation.

Encouraged by the preliminary result, enantioselective mesylation, which has a broad synthetic use as well, was examined under the same conditions. However, due to the formation of a sulfene intermediate, which is extremely unstable and reactive, the reaction showed no enantioselectivity (Figure 7).[30]

Figure 7

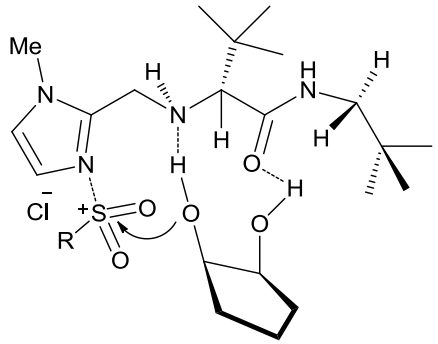


Later, the loading of the catalyst was reduced and DIPEA was used as a base to regenerate the catalyst (Eq. 2).



Eq. 2

Based on all of the observations above, one possible transition state is shown in Scheme 2.3.



Scheme 2.3. Proposed Transition State Model for Catalytic Enantioselective Tosylation of Diols

[30] (a) Skrypnik, Y. G.; Lyashchuk, S. N. *Sulfur Letters*. **1994**, *17*, 287-294; (b) King, J. F.; Lewars, E. G. *Canadian Journal of Chemistry*. **1973**, *51*, 3044-3050; (c) Truce, W. E.; Campbell, R. W. *J. Am. Chem. Soc*. **1966**, *88*, 3599-3604.

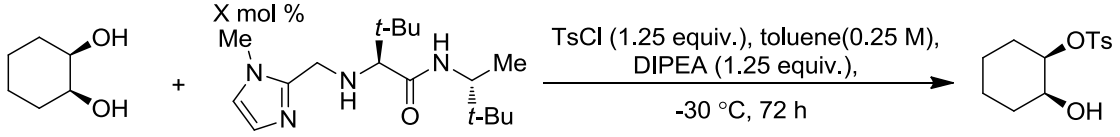
After the feasibility of enantioselective tosylation of *meso*-diols by single-amino-acid based Lewis basic catalyst **2.1** was proven, work was focused on optimization of the reaction conditions and modification of the catalyst.

2.3 Reaction Condition Optimization

Catalyst loading

In a catalytic enantioselective reaction, the amount of catalyst needed is an important factor in determining the practicality of the methodology, especially when the catalyst requires many steps to make or its price is high.[31] Therefore, catalyst loading for this enantioselective tosylation was examined, which is shown in Table 2.1.

Table 2.1. Catalyst Loading Study of Catalytic Enantioselective Tosylation



Entry	cat. (mol %)	Yield (%)[a]	*ee* (%)
1	5	<5	53
2	10	22	58
3	20	37	58
4	30	56	72
5	50	58	79

[a] Conversion was determined by NMR internal standard (Acetophenone).

It can be seen that as an increasing amount of the catalyst is used, the enantioselectivity of the reaction improves; the same trend is seen for the yield of the mono-tosylate (entry 1, 2, 3 and 4).

---

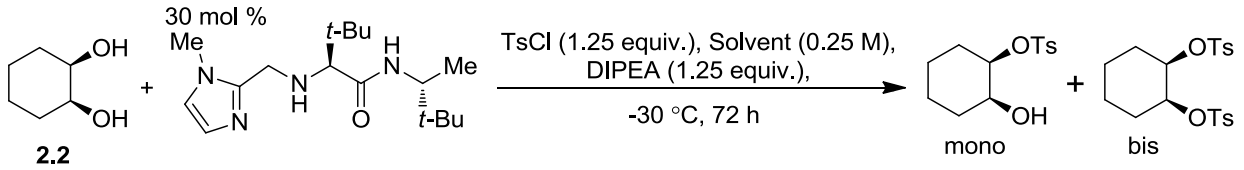
[31] (a) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev.* **2007**, *107*, 5841-5883; (b) Bartok, M. *Chem. Rev*. **2010**, *110*, 1663-1705.

When the catalyst loading is increased from 30 mol % (entry 4) to 50 mol % (entry 5), however, neither the *ee* nor the yield of the desired product increase significantly. One possible explanation is that the solubility of the catalyst in toluene is limited. Even though 50 mol % of the catalyst was added, only a portion of it dissolved and became involved in the catalytic cycle. Therefore, 30 mol % catalyst loading was chosen as optimal.

Solvent Effect

Solvent has a critical effect not only on the reaction rate and yield,[32] but also on the enantioselectivity due to its impact on activation energies.[33] For enantioselective tosylation, a series of commonly used solvents were tested to find the optimal one (Table 2.2).

Table 2.2. Solvent Effect Study of Catalytic Enantioselective Tosylation

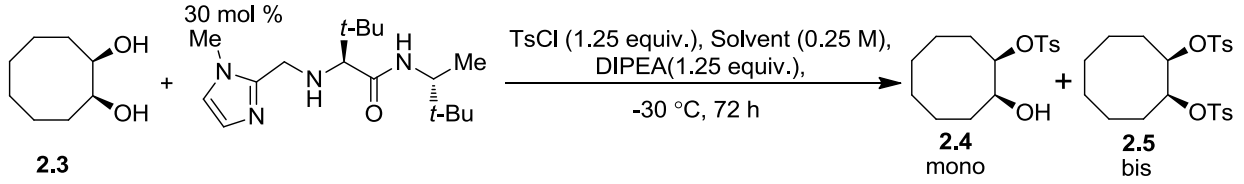


Entry	Solvent	conversion (%)	*ee* (%)	mono/bis
1	toluene	60	76	1:0.3
2	THF	40	56	>10
3	Et_2O	43	88	1:0.6
4	*t*-BuOMe	62	88	1:0.4
5	EtOAc	27	59	>10
6	CH_2Cl_2	30	16	1:0.2
7	CH_3CN	19	34	1:0.2
8	DMF	<5	-	-

[32] Li, C.; Du, M. *Chem. Comm*. **2011**, *47*, 5958-5972.
[33] Subramanian, V. *Chemical Reactivity Theory*. Tayler & Francis Group, LLC, Florida, **2009**, pp. 379-393.

Generally, acyclic ether solvents give the best enantioselectivity (entry 3 and 4). In toluene (entry 1), even though the enantioselectivity is not as high as in ether, the conversion is good. In very polar solvents, such as THF (entry 2), CH_3CN (entry 7) and DMF (entry 8), both the conversion and the enantioselectivity are poor. Another interesting observation is that for all of the cases that have high enantioselectivity, the mono/bis ratio is low. For instance, in toluene, the reaction gives 76% *ee*, while the mono/bis ratio is 1: 0.3; in Et_2O and *t*-BuOMe, the *ee*'s are both 88% and the mono/bis ratios are 1: 0.6 and 1: 0.4 respectively. A similar solvent effect was also observed with *meso*-1,2-diol **2.3**.

Table 2.3. Solvent Effect Study of Catalytic Enantioselective Tosylation

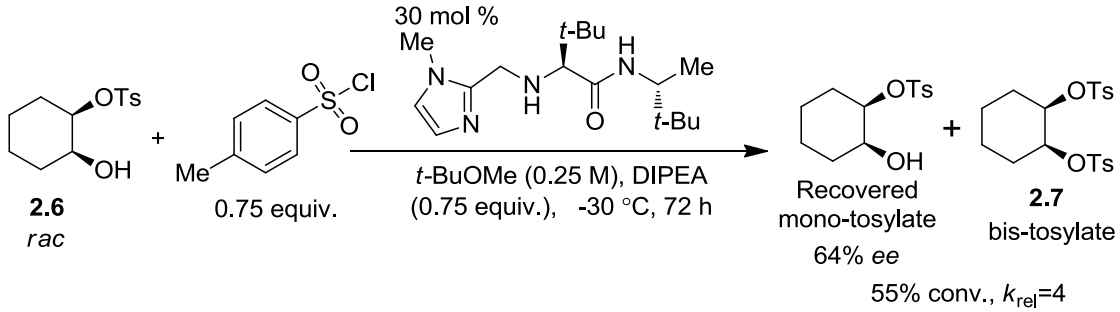


Entry	Solvent	conversion (%)	*ee* (%)	mono/bis
1	Et_2O	92	59	1:0.1
2	THF	53	35	>10:1
3	2,5-dimethyl-tetrahydrofuran	52	53	>10:1
4	EtOAc	65	43	>10:1
5	toluene	94	55	>10:1
6	CH_2Cl_2	57	-3	>10:1
7	*t*-BuOMe	89	64	1:0.13

In Table 2.3, it can be seen that Et_2O and *t*-BuOMe provide the best enantioselectivities (Entry 1 and 7), while toluene, Et_2O, and *t*-BuOMe, give the highest conversions. Interestingly, the cases that give the best enantioselectivity also have more bis-tosylate **2.5**, which coincides with the trend in Table 2.2.

Kinetic Resolution of *rac*-mono-Tosylate

To rationalize the trend that exists between the high enantiopurity of the mono-tosylate and the high bis-tosylate formation, a kinetic resolution of racemic mono-tosylate **2.6** was designed.[34, 35] The enantioselective tosylation reaction was set up in *t*-BuOMe at -30 ℃ for 3 days, as shown in Eq. 3.



Eq. 3

Based on the result of the kinetic resolution study, the undesired mono-tosylate enantiomer reacts faster with TsCl in the presence of catalyst, which enriches the desired mono-tosylate enantiomer and improves the enantioselectivity of the tosylation reaction.

Concentration and Temperature Evaluation

In the proposed mechanism of catalytic desymmetrization of *meso*-diols, the catalyst interacts with the alcohols through hydrogen bonding.[36] The factor that most influences the strength of a hydrogen bond formed between catalyst and diols is the solvent. The solvent dramatically influences the strength of the hydrogen bond because the donor and acceptor are solvated prior to formation of the hydrogen bond. Because of the important effect of solvation, concentration has a big influence on the strength of hydrogen bonding interactions between catalyst **2.1** and diols. To evaluate the influence of reaction concentration on the

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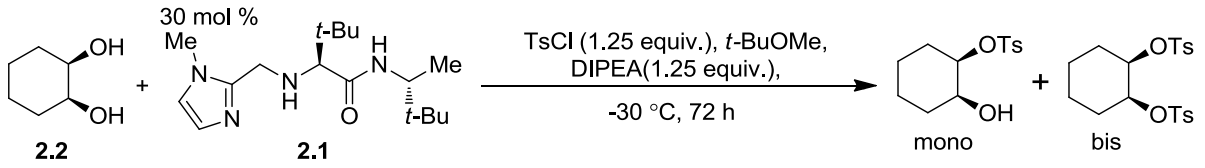
[34] (a) Lee, J. H.; Han, K.; Kim, M.; Park, J. *Eur. J. Org. Chem*. **2010**, *6*, 999-1015; (b) Baeckvall, J. E. *Asymmetric Synthesis*, 2nd ed., **2008**, 179-184.
[35] Rendler, S.; Oestreich, M. *Angew. Chem. Int. Ed*. **2008**, *47*, 248-250.
[36] Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*. University Science Books, California, **2006**, pp. 171.

enantioselectivity, a few different concentrations were tested (Table 2.4).

Table 2.4. Concentration Study of Catalytic Enantioselective Tosylation



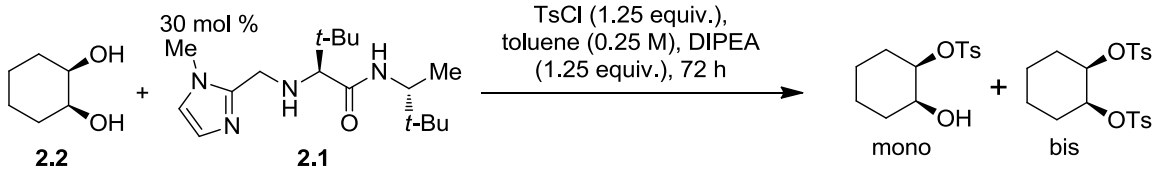
Entry	Concentration	conversion (%)	*ee* (%)	mono/bis
1	0.13 M	45	48	1:0.13
2	0.25 M	89	83	1:0.30
3	0.33 M	64	80	1:0.22
4	0.50 M	66	84	1:0.35
5	1.0 M	53	84	1:0.46

Increasing the concentration of the reaction did improve the enantioselectivity at low concentration (Entries 1 and 2); however, further increasing the reaction concentration did not further improve the enantioselectivity, while the conversion and mono/bis-tosylate ratio suffered (Entries 3, 4 and 5). This observation could be attributed to the poor solubility of both the diol and the catalyst at -30 ℃ in *t*-BuOMe. Since the reaction mixture was heterogeneous, the real concentration in solution was lower than expected. Because of the limited solubility of starting material, the conversion of the reaction was damaged and the *ee* did not improve further. Due to the better solubility of the mono-tosylate over the diol in *t*-BuOMe, at high concentrations, the mono-tosylate has more chance to interact with the catalyst and to undergo secondary tosylation, which explains the high bis-tosylate formation at high concentrations.

The effect of temperature was also studied due to its expected significant influence on the rate and enantioselectivity of the catalyzed reaction (Table 2.5).[37]

[37] Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*. University Science Books, California, **2005**, Chapter 9.

Table 2.5. Temperature Study of Catalytic Enantioselective Tosylation



2.2 2.1

Entry	Temp. (°C)	Yield (%)	*ee* (%)
1	-15	78	70
2	-30	55	77
3	-50	27	84
4	-78	<5	-

Lowering the reaction temperature helped to improve the enantioselectivity of the reaction (Entries 1, 2 and 3). Unfortunately, the reaction rate decreased significantly. At -50 ℃, the yield of mono-product is only half of that at -30 ℃. At -78 ℃, the conversion is so low that the product can barely be identified by NMR of the crude reaction mixture; -30 ℃ was therefore chosen as the optimal temperature for the catalytic enantioselective tosylation.

Base Optimization

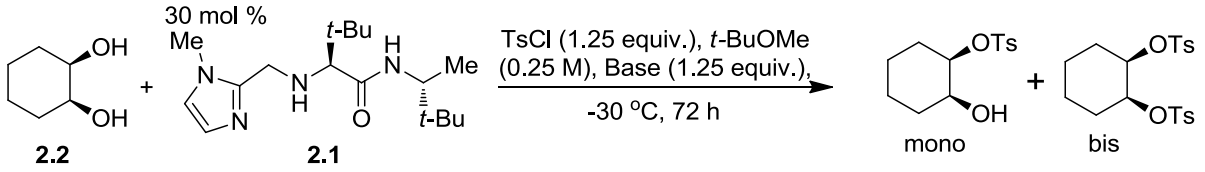
To improve further the yield and enantioselectivity of the reaction, organic bases including tertiary amines, aniline derivatives, pyridine derivatives and inorganic bases were screened. Before carrying out the base screens, the background reaction was first examined without adding catalyst. Table 2.6 shows that in the absence of catalyst, for all of the bases examined, there was no conversion, which excluded any general base catalyzed processes.

Table 2.6. Background Study of Bases

Entry	Base	Conversion (%)
1	DIPEA	NR
2	Proton Sponge	NR
3	2,6-Lutidine	NR
4	2,6-Di-tert-butylpyridine	NR
5	N,N-Dimethylaniline	NR

. Each base was then tested in the catalytic enantioselective tosylation reaction. The results are shown in Table 2.7.

Table 2.7. Base Evaluation of Catalytic Enantioselective Tosylation



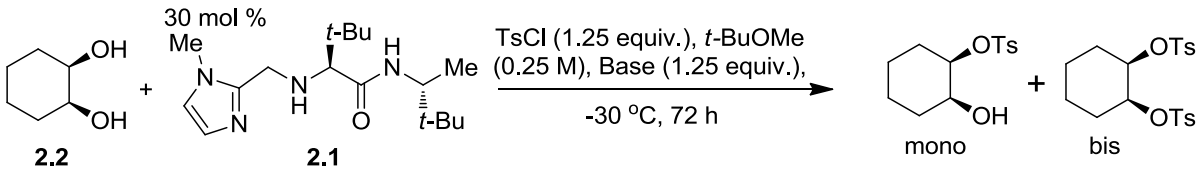
Entry	Base	Conversion (%)	*ee* (%)	mono/bis
1	DIPEA	86	84	1:0.27
2	TEA	39	48	1:0.25
3	Proton Sponge	59	83	1:0.22
4	N,N-Dimethylaniline	31	83	>10
5	Pyridine	27	58	>10
6	2,6-Lutidine	51	79	>10
7	DBU	48	48	1:0.35

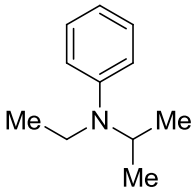
DIPEA provides the best enantioselectivity and conversion (Entry 1). Triethylamine, gives lower enantioselectivity and conversion (Entry 2). When using proton sponge, the reaction achieved good enantioselectivity, but lower conversion. *N*,*N*-dimethylaniline, pyridine and 2,6-lutidine (Entries 3, 4 and 5) are all weak bases compared to DIPEA (protonated form: pKa=10.7) and proton sponge (protonated form: pKa=12).[38] The pKa's of protonated *N*,*N*-dimethylaniline, pyridine and 2, 6-lutidine are 5.2, 5.2, 6.8 respectively. Since the catalyst has a secondary amine moiety, which can serve as a strong base for deprotonation, the pKa of the added base has to be larger than the pKa of a secondary amine unless the base salt formed precipitates.

[38] pKa data were referred to (a) Evan's pKa table (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 4th ed., Wiley, New York, **1985**.

In the catalytic cycle, we hypothesized that it is the secondary amine in the catalyst that first deprotonates the substrate or its intermediate, then the added base helps to remove the proton from the protonated catalyst and recover the catalyst. If the added base is a weaker base than a secondary amine, the catalyst will remain protonated and be removed from the catalytic cycle. Since 30 mol % catalyst is used in the reaction, the conversion should stop at 30%. To support this hypothesis, and to systematically find out the relationship between base structure and its impact on the reaction, a series of aniline derivatives with different steric hindrances were examined in the enantioselective tosylation reaction (Scheme 2.4).

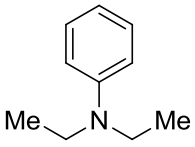
Scheme 2.4. Base Evaluation of Catalytic Enantioselective Tosylation





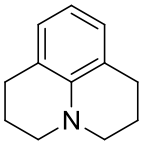
2.8

32% conv.
78% *ee*
mono:bis >10



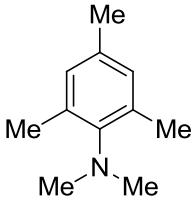
2.9

20% conv.
79% *ee*
mono:bis >10



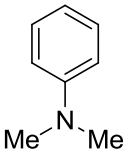
2.10

38% conv.
77% *ee*
mono:bis >10



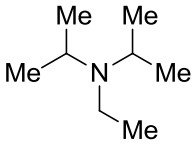
2.11

31% conv.
80% *ee*
mono:bis >10



2.12

30% conv.
80% *ee*
mono:bis >10



2.13

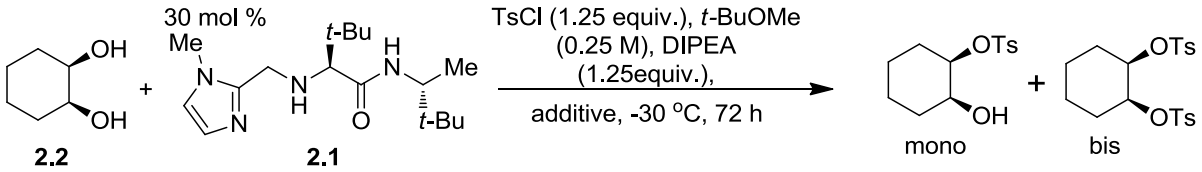
70% conv.
84% *ee*
mono: bis= 1:0.27

All of the chosen aniline derivative bases in this screen have a pKa around 5. Even though the steric hindrance of each base varies significantly, they all give around 30% conversion with more than 10:1 mono/bis-tosylate ratio. The enantioselectivities of these reactions are quite similar as well. This supports the hypothesis that the secondary amine in the catalyst is involved in the deprotonation of the substrate or its intermediate during the tosylation reaction.

Also, even when relatively strong bases were used, different enantioselectivities could be achieved. For example, triethylamine led to 48% *ee* (Entry 2 in Table 2.7) while DIPEA provided 84% *ee* (Entry 1 in Table 2.7). From this observation, it can be concluded that the base may not only act as a base, but it might also be involved in the enantiodetermining step.

To promote the deprotonation step, inorganic bases were applied as additives (Table 2.8).[39]

Table 2.8. Evaluation of Inorganic Base as Additive



Entry	Inorganic base	Conversion (%)	*ee* (%)	mono/bis
1	None	72	83	1:0.33
2	$NaHCO_3$	78	80	1:0.35
3	$CsCO_3$	32	60	>10
4	K_2CO_3	82	82	1:0.31
5	KOH	68	63	1:0.43

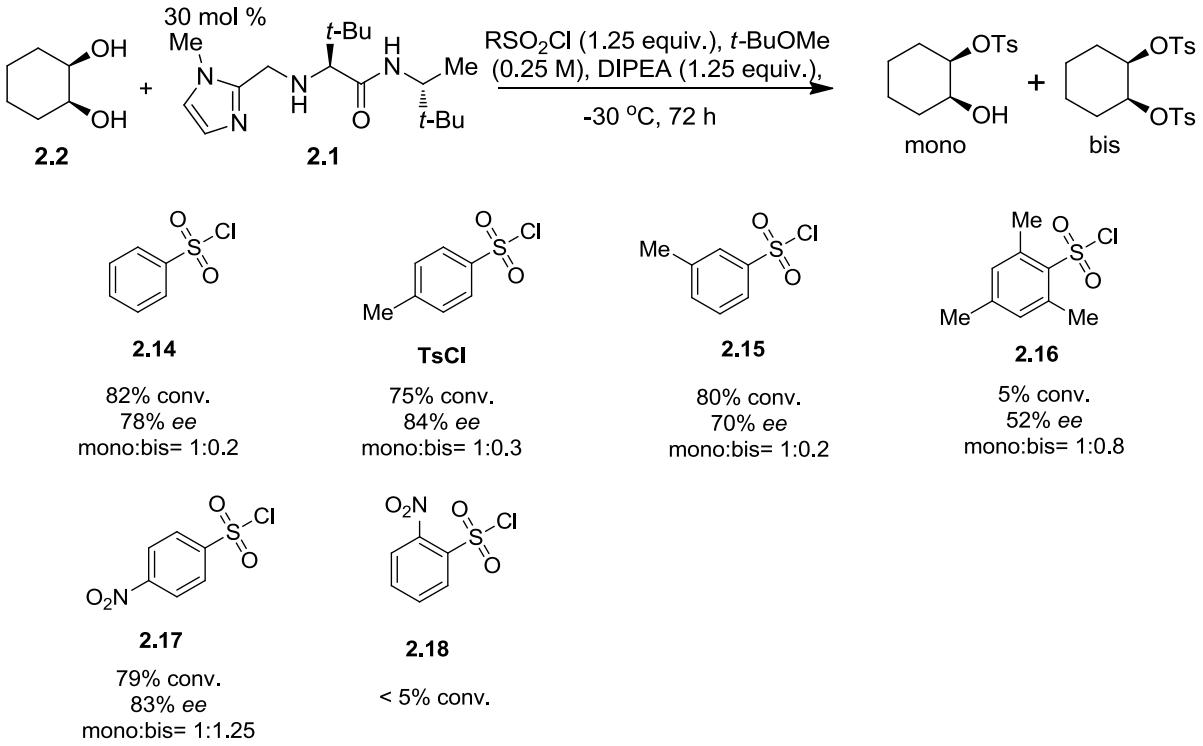
Generally, the inorganic base additives were not helpful in improving the enantioselectivity and reaction rate. This may be due to their poor solubilities in *t*-BuOMe.

[39] (a) Wang, Y.; Li, P.; Liang, X.; Ye, J. *Adv. Synth. Catal*. **2008**, *9*, 1383-1389; (b) Flessner T.and Doye, S. *J. Prakt. Chem*. **1999**, *341*, 186-190; (c) Forryan, C. L.; Klymenko, O. V.; Brennan, C. M.; Compton, R. G. *J. Phys. Chem. B*, **2005**, *109*, 8263-8269.

Sulfonylation Reagent Study

In addition to tosyl chloride, some other arene sulfonylation reagents were tested for enantioselective sulfonylation with catalyst **2.1** and *meso*-diol **2.2** as the test substrate (Scheme 2.5).

Scheme 2.5. Sulfonylation Reagent Study of Catalytic Enantioselective Tosylation



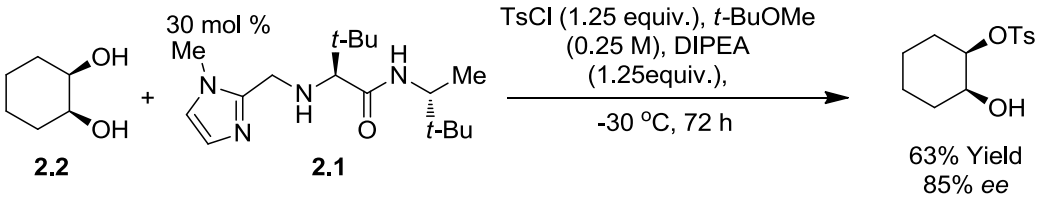
The use of benzenesulfonyl chloride (**2.14**) in the reaction gave better conversion and mono/bis-sulfonylate selectivity (82% conversion and 1:0.2 mono/bis ratio) than TsCl (75% conversion and 1:0.3 mono/bis ratio). The enantioselectivity, however, was lower than that of the reaction with TsCl (78% *ee* versus 84% *ee*). *m*-Toluenesulfonyl chloride (**2.15**) gave similar results. The use of 2,4,6-trimethylbenzenesulfonyl chloride (**2.16**) and *o*-nitrobenzenesulfonyl chloride (**2.18**) led to poor conversion, which might be due to the difficult-access of the sulfonyl group caused by the steric hindrance of ortho substituents. When using *p*-nitrobenzenesulfonyl chloride (**2.17**), the conversion was high and the *ee* of the mono-nosylate product was very close

to the *ee* of the mono-tosylate product. Due to the electron withdrawing nature of the nitro group, *p*-nitrobenzenesulfonyl chloride (**2.17**) is much more reactive than *p*-toluenesulfonyl chloride, this leads to the full consumption of *p*-nitrobenzenesulfonyl chloride (**2.17**) in the reaction and shortens the reaction time significantly; however, the use of *p*-nitrobenzenesulfonyl chloride (**2.17**) as the sulfonylation reagent leads to an unfavorable mono/bis-sulfonylate ratio.

Since NsCl (**2.17**) is very reactive at -30 ℃, this leaves room for the modification of the conditions of enantioselective nosylation. Unfortunately, neither decreasing the amount of NsCl nor lowering the reaction temperature helped to improve the mono/bis-nosylate ratio. So far, tosyl chloride is still the best sulfonylation reagent in our catalytic enantioselective sulfonylation reaction.

Conclusion of Condition Modifications

After screening concentrations, temperatures, solvents, additives, bases and sulfonylation reagents, the best conditions developed so far for the catalytic enantioselective sulfonylation of *meso*-1,2-cyclohexanediol (**2.2**) are using 1.25 equiv. tosyl chloride, 1.25 equiv. DIPEA and 30 mol % catalyst **2.1** in *t*-BuOMe at -30 ℃ for 3 days. Under these conditions, 85% *ee* and 63% isolated yield of the mono-tosylate can be achieved (Eq. 4).



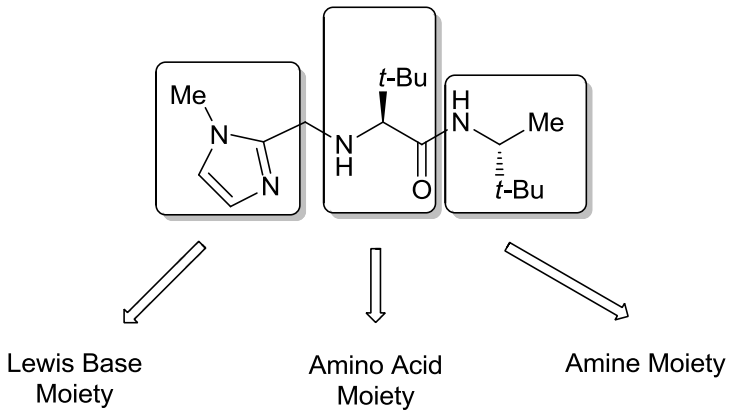
2.2 2.1

Eq. 4

2.4 Modification of the Catalyst

Catalyst **2.1** used in the enantioselective sulfonylation reaction was used in the enantioselective silylation, which was developed by previous group members Dr. Yu Zhao and Dr. Jason Rodrigo. The catalyst was synthesized by combining three segments together: a Lewis-base moiety, an amino acid moiety and an amine moiety (Scheme 2.6).

Scheme 2.6. Structure Analysis of Tosylation Catalyst



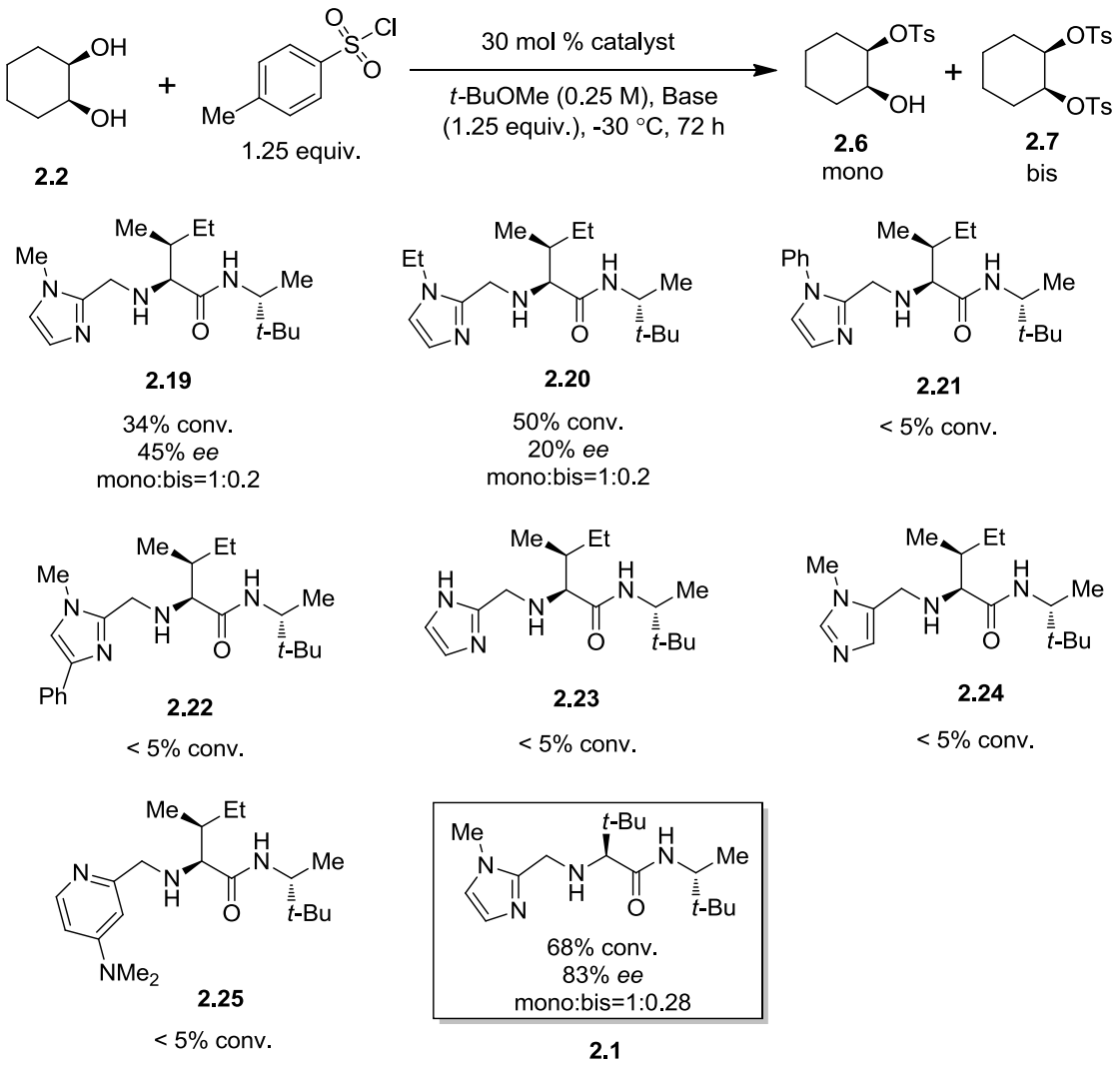
Therefore, modifications to this catalyst were approached as systematic changes to each segment.

Modification of Lewis Base

Some of the most commonly used Lewis bases are imidazole derivatives and 4-dimethylaminopyridine (DMAP). Both of these two types of Lewis bases were integrated into the amino-acid-based catalyst (Scheme 2.7). The amino acid used in the evaluation of different Lewis bases was *L*-isoleucine. Catalyst **2.19** was the control catalyst. Comparing the results of catalysts **2.19**, **2.20** and **2.21**, substituents on the nitrogen of the imidazole ring affected the conversion and enantioselectivity significantly. Ethyl-substituted imidazole catalyst **2.20** gave better conversion but poor enantioselectivity. Catalyst **2.21** gave almost no conversion, which could be due to the electron withdrawing character of the phenyl group, leading to poor

activation of the TsCl, or the catalyst's most stable conformation is not conducive to efficient interaction with the diol. The alkyl substituent on the imidazole ring is necessary for catalysis. Remove the methyl group led to a catalyst with no reactivity (**2.23**). This might be due to the electron donating character of the methyl group, which enhances the nucleophilicity of the imidazole ring, hence increasing the reactivity of the catalyst. Extra substituents on the imidazole ring (**2.22**) and different pattern of connection between the *N*-methylimidazole and the amino-acid backbone (**2.24**) led to poor conversion. The use of DMAP as a Lewis base also damaged the reactivity of the catalyst in enantioselective tosylation (**2.25**).

Scheme 2.7. Lewis Base Moiety Modification of Tosylation Catalyst

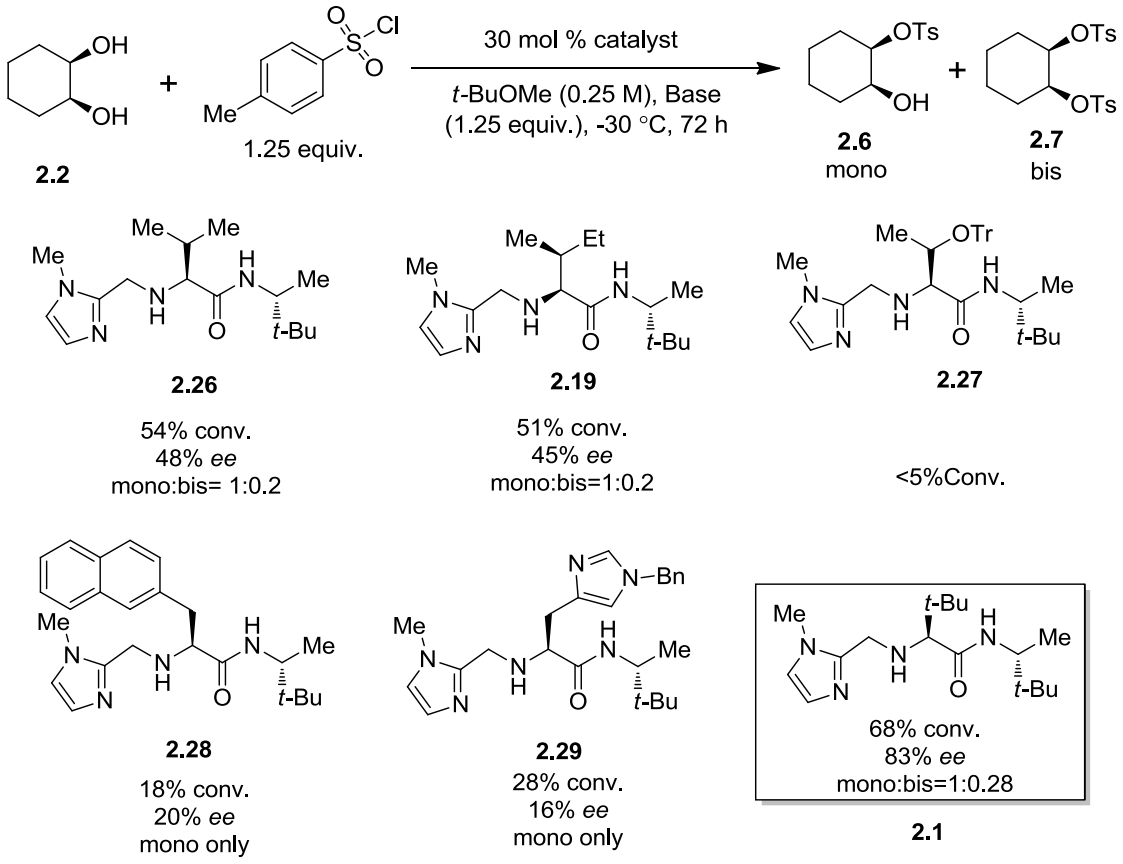


The screen in Scheme 2.7 shows that *N*-methylimidazole is the best Lewis base catalytic moiety in our amino-acid-based catalyst.

Modification of the Amino Acid

The chiral amino acid is key to the catalyst as it introduces the enantioselectivity in the tosylation reaction. A variety of chiral amino acids were tested with *N*-methylimidazole as the Lewis base and (*R*)-3,3-dimethylbutan-2-amine as the chiral amine (Scheme 2.8).

Scheme 2.8. Amino Acid Moiety Modification of Tosylation Catalyst



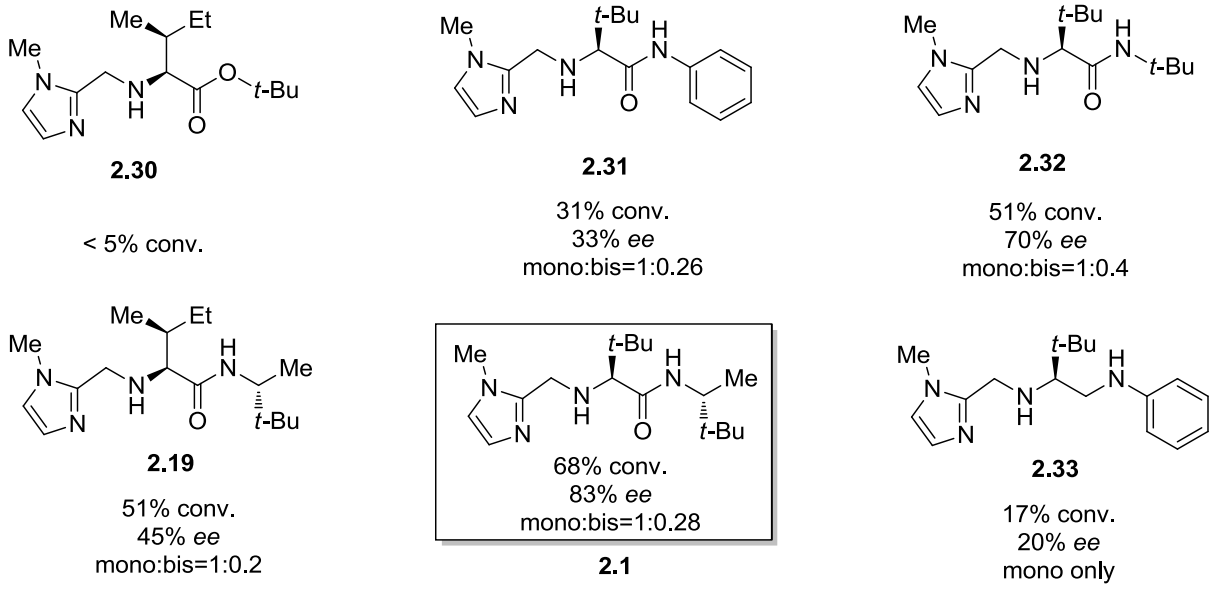
Generally, the screen of the amino acid moiety shows that the more sterically hindered the amino acid in the catalyst is, the better the enantioselectivity and conversion. In catalyst **2.28** and **2.29**, both amino acid moieties have a primary substituent that leads to very poor the conversion and *ee* (18% conversion, 20% *ee* for catalyst **2.28**; 28% conversion, 16% *ee* for catalyst **2.29**).

When amino acids with secondary substituent were used in the tosylation catalyst, both the conversion and mono-tosylate *ee* had significant improvement. Catalyst **2.26** with *L*-valine provides 54% conversion and 48% *ee*, while catalyst **2.19** with *L*-leucine leads to 51% conversion and 45% *ee*. Also, these two catalysts provide very similar mono/bis-tosylate ratios. This could all be attributed to the similarity between the two amino acids. Catalyst **2.27** also has an amino acid with a secondary carbon substituent, however, the reactivity drops significantly compared to catalysts **2.16** and **2.19.** This might be due to the large size of the triphenylmethyl (Tr) group, causing the most stable conformation of the catalyst to be less ideal for the desymmetrization of diols. Following this trend, when a tertiary carbon substituent as the side chain of the amino acid was introduced into the catalyst, the enantioselectivity and conversion both improved, and the best tosylation results so far were achieved.

Modification of Amide

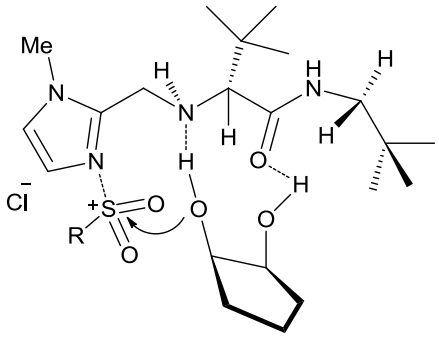
As the chiral amide group in the catalyst is another moiety that can introduce and enhance the enantioselectivity in the tosylation reaction, modifications of the amide group were carried out (Scheme 2.9).

Scheme 2.9. Amide Moiety Modification of Tosylation Catalyst



When the chiral amide moiety was replaced with an achiral one, the enantioselectivity of the catalyst and the reaction rate dropped (**2.1** versus **2.31** and **2.32**). This tells us the chiral substituent of the amide helps to improve the overall enantioselectivity and conversion of the tosylation reaction. Also, it seems that bulker substituents on the amide provide better product *ee* and reaction conversion (**2.31** versus **2.32**). Once the amide group was changed to an ester group, however, the catalyst showed barely any reactivity in tosylation, giving less than 5% conversion for 3 days reaction time at -30 ℃. One explanation for this is that the amide group is a key hydrogen bond acceptor in the desymmetrization reaction (Figure 8). The amide is a better hydrogen bond acceptor than the ester due to the better donating ability of the lone pair electrons on nitrogen than those on oxygen. Reduction of catalyst **2.31** gave catalyst **2.33** without an amide group. This modification leads to worse enantioselectivity and reactivity, which supports the importance of the amide group in the catalyst as a hydrogen bond acceptor.

Figure 8



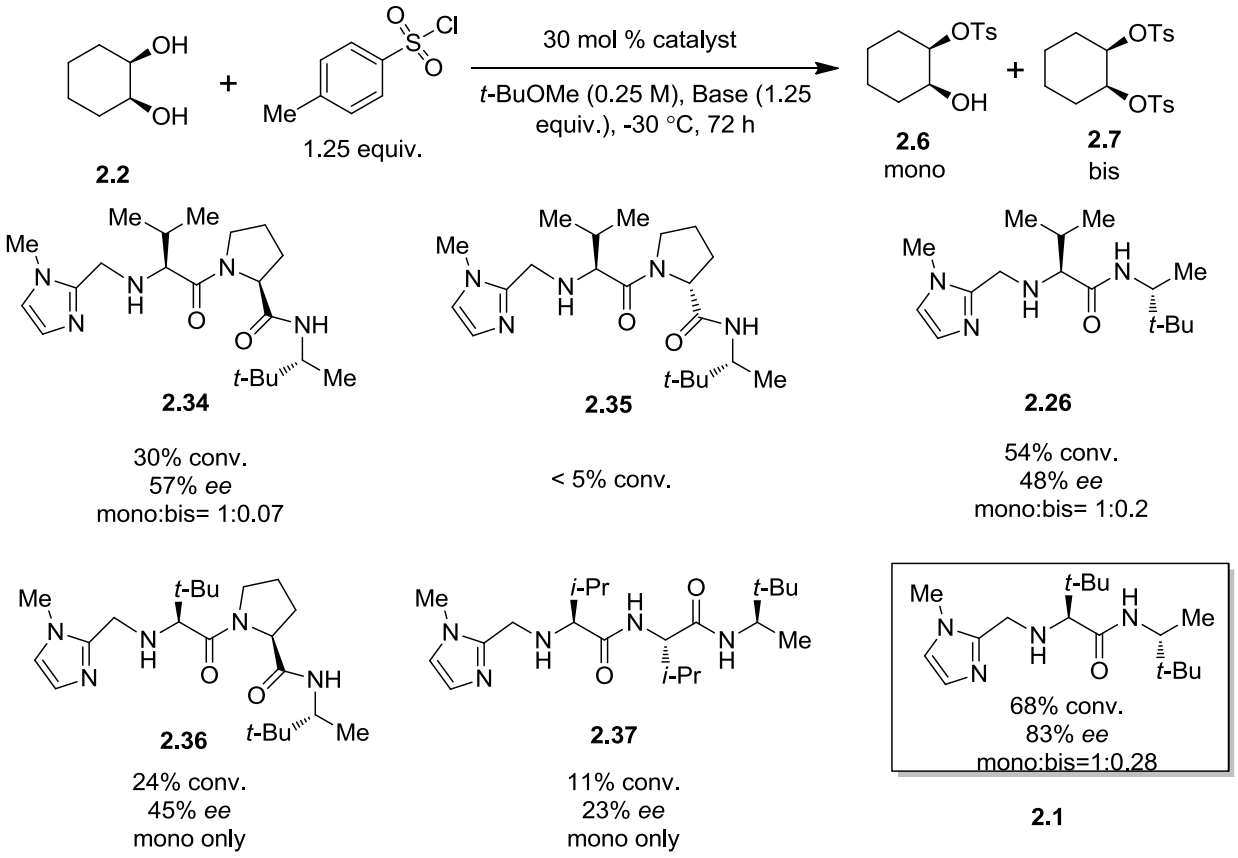
Diamino-Acid-Based Modifications

Inspired by the hypothesis that the catalyst desymmetrizes the diol through hydrogen bonding interactions, some diamino-acid-based catalysts were synthesized. Since these catalysts had more amide bonds that could be hydrogen bond acceptors or donors, we hoped they could provide stronger hydrogen bonding interactions and consequently improve the enantioselectivity of the reaction (Scheme 2.10).

Catalyst **2.37** was first synthesized, but it only provided 11% conversion and 23% *ee*. By contrast, the control catalyst **2.26** gave 54% conversion and 48% *ee*. The failure of **2.37** could be

due to the added amide bond not participating in hydrogen bonding. It is also possible that catalyst **2.37** is too linear, which means it needs to pay a larger entropy cost to efficiently interact with the diol, this could lead to low reactivity and selectivity.

Scheme 2.10. Diamino-Acid-Based Modification of Tosylation Catalyst



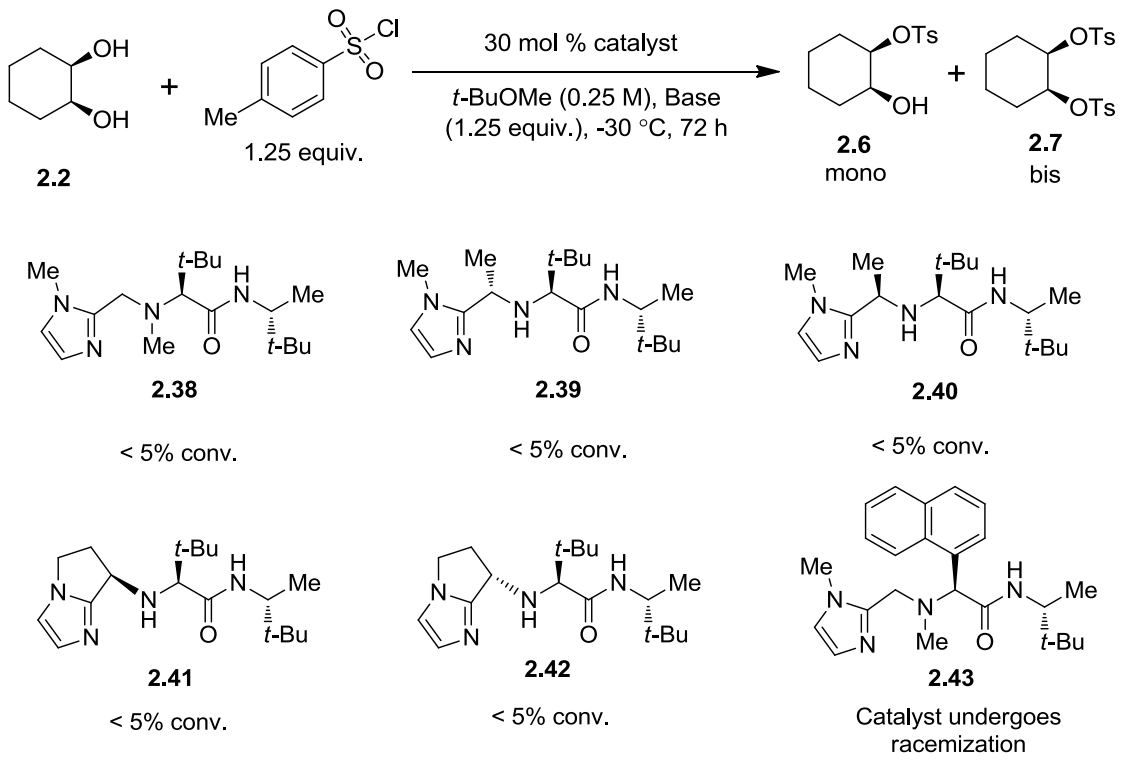
Catalysts **2.34** and **2.35** were made using proline to replace valine to force the catalyst's conformation to be bent by the rigid five-membered ring of proline. Through this, the amide groups in the catalyst were brought closer together so as to interact with the diol and to avoid increasing the entropy cost during the catalytic transition state. For catalyst **2.34**, a slight improvement in enantioselectivity was observed, while the conversion decreased compared with the reaction catalyzed by the control catalyst **2.26**.

However, less than 5% conversion was seen when catalyst **2.35** was applied in the tosylation reaction. This could be explained by the very poor solubility of catalyst **2.35** in *t*-BuOMe due to intermolecular hydrogen bonding with another catalyst.

Even though some improvement was observed when introducing a proline into the catalyst, this was not the case when catalyst **2.36** was made by incorporating a proline moiety into the control catalyst **2.1**. Catalyst **2.36** led to worse conversion and enantioselectivity than catalyst **2.1**. The reason for this observation is not quite clear.

Other Modifications

Scheme 2.11. Modification of Tosylation Catalyst

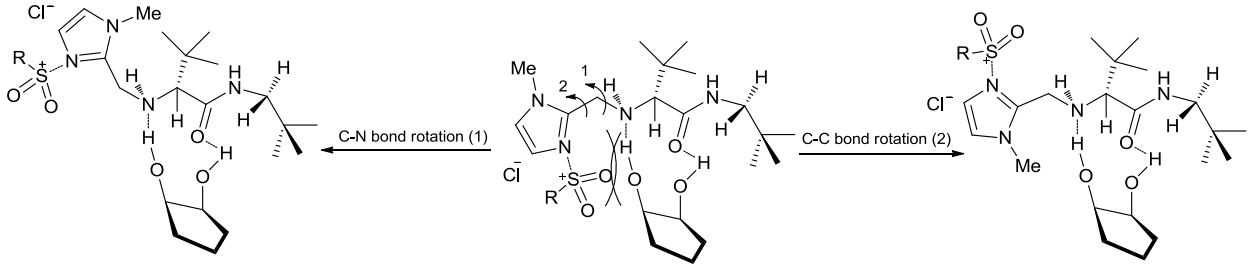


Additional catalyst modifications were carried out and are shown in Scheme 2.11. Catalyst **2.38** was made by introducing a methyl group on the secondary amine; it showed no reactivity. Since the secondary amine is involved in hydrogen bonding, the methyl group on nitrogen blocks

this interaction. Methyl groups were also introduced into the allylic position of the *N*-methylimidazole (**2.39** and **2.40**), but these modifications also led to catalysts with no reactivity.

Besides improving the enantioselectivity of the catalyst in tosylation, improving the reaction rate and shortening the reaction time are also primary concerns. For catalyst **2.1**, the low catalytic activity can be explained by the fact that, C-C bond **2** and C-N bond **1** are free to rotate since they are sp^3 bonds (Scheme 2.5). Once the catalyst forms the catalyst-diol complex through hydrogen bonding, the steric hindrance between diol and the activated sulfonyl chloride will force the C-C or C-N bond to rotate, leading to unreactive conformations of catalyst-substrate complex (Scheme 2.12). To get sulfonylation to take place, a higher activation energy is needed to overcome the steric repulsion and to bring the diol and the activated sulfonyl chloride close, which explains the low reactivity.

Scheme 2.12. Reduction of Catalyst Activity Due to sp^3 Bond Rotation



Based on this hypothesis, catalyst **2.41** and **2.42** were synthesized. The rigidity of the five-membered ring fused to the imidazole ring keeps the C-C and C-N bonds from freely rotating. Since another stereocenter was introduced into the catalyst, both diastereomers were tested to determine which, if any, would improve the enantioselectivity. Unfortunately, neither of the two catalysts showed any reactivity.

Later, catalyst **2.43** was made, based on the thought that a larger substituent on the amino acid would block the free rotation of the C-C and C-N bonds in order to avoid steric repulsion

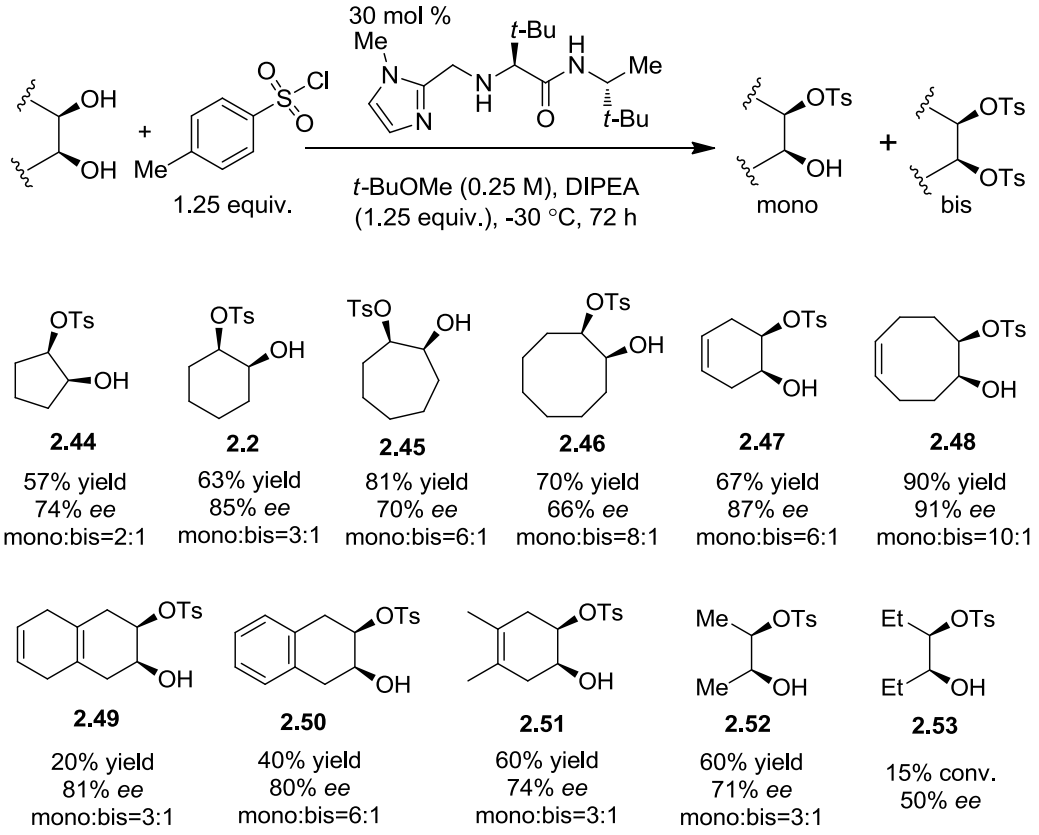
between the amino acid substituent and the activated sulfonyl complex. However, because of the strong acidity of the tertiary proton in the amino acid, racemization of the amino acid moiety was observed for catalyst **2.43;** this strongly diminished its enantioselectivity and its practicality.

2.5 Substrate Scope

With the modified reaction conditions and the optimized catalyst thus far designed, the catalytic enantioselective tosylation methodology was applied to more cyclic and acyclic substrates, including *meso*-1,2-diols, *meso*-1,3-diols and *cis*-*meso*-1,2,3-triols.

meso-1,2-diols

Scheme 2.13. *meso*-1,2-Diol Scope of Catalytic Enantioselective Tosylation

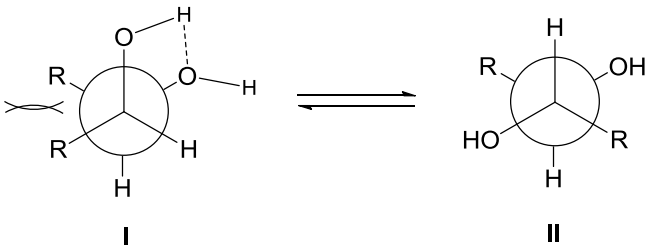


Generally, for saturated monocyclic *meso*-1,2-diols (**2.44, 2.2, 2.45** and **2.46**), a larger ring size leads to better mono/bis ratio, but poorer enantioselectivity (Scheme 2.13). Overall, unsaturated monocyclic *meso*-1,2-diols (**2.47** and **2.48**) undergo better desymmetrization than

saturated counterparts, and give better mono/bis ratios as well. When *meso*-1,2-cyclooctenediol (**2.48**) was tested in the enantioselective tosylation, the mono-tosylate was afforded in 90% yield and 91% *ee*. Disubstituted *meso*-1,2-cyclohexenediols (**2.49**, **2.50** and **2.51**) led to products with similar ee's. This shows that substituents on the olefin do not affect the desymmetrization of the diols, which may be a result of the long distance between the substituents and the catalyst in the transition state. The yield of the mono-tosylate decreases, however, when the size of the substituent increases.

When acyclic *meso*-1,2-diols are used as substrates, the size of the R group geminal to the hydroxyl group is critical. When the R group is a methyl group, the enantioselective tosylation proceeds smoothly. Replacing the methyl with an ethyl group, however, leads to a sharp drop in reaction conversion and mono-tosylate *ee*. One hypothesis to explain this is that the preferred conformation of acyclic *meso*-1,2-diols is determined by two opposing forces: intramolecular hydrogen bonding and gauche repulsion of the two R groups. When the R group is small, intramolecular hydrogen bonding is the main force, and conformation **I** is favored (Figure 9). Since in this conformation the two hydroxyl groups are close to each other, it is easy for the catalyst to interact through hydrogen bonding and catalyze tosylation. When the R group is large, gauche repulsion is the dominant factor, and conformation **II** is preferred, when the two hydroxyl groups are anti to each other. This prevents the diol from building up efficient interaction with the catalyst through hydrogen bonding, hence affording poor yield and enantioselectivity.

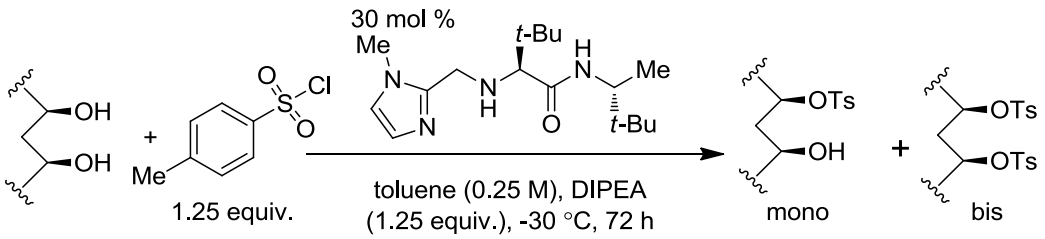
Figure 9



***meso*-1,3-diols**

1,3-Diol transformations have more synthetic applications than those of 1,2-diols. Cyclic and acyclic *meso*-1,3-diols were examined under this methodology (Scheme 2.14).

Scheme 2.14. *meso*-1,3-Diol Scope of Catalytic Enantioselective Tosylation

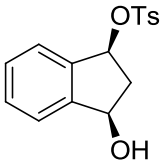


2.54

58% yield
46% *ee*
mono:bis=10:1

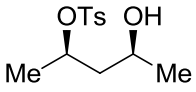
2.55

67% yield
64% *ee*
mono:bis=10:1



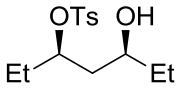
2.56

No conv.



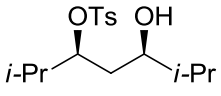
2.57

64% yield
79% *ee*
mono:bis=2.5:1



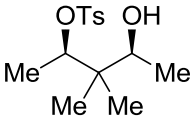
2.58

19% yield
60% *ee*
mono:bis=10:1



2.59

< 5% conv.



2.60

20% yield
37% *ee*
mono only

During screening of enantioselective tosylation of *meso*-1,3-diols, toluene rather than *t*-BuOMe was found to be the optimal solvent for both cyclic and acyclic diols. For *cis*-1,3-cyclopentanediol (**2.54**) and *cis*-1,3-cyclohexanediol (**2.55**), the catalytic reaction gave 58 and 67% yield and 46 and 64% *ee* respectively. *cis*-1,3-Cyclopentenediol was tested as well but no mono-tosylate was detected, possibly due to the decomposition of the unstable allylic tosylate. More structural complicated *cis*-1,3-indenediol (**2.56**) did not afford any desired product.

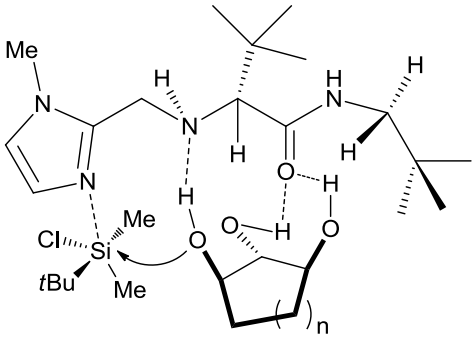
For acyclic *meso*-1,3-diols, the larger the substituent geminal to the hydroxyl group, the worse the substrate is for this catalytic tosylation transformation. When the geminal group is a methyl group (**2.57**), the reaction runs smoothly and gives 64% yield and 79% *ee*. One thing worthy to note is that this reaction is complete in 24 h, which is much faster than the reaction with other substrates. This could be due to the very good solubility of **2.57** in toluene, leading to a high concentration of diol in solution, which promotes the formation of the catalyst-substrate complex. If the geminal group is ethyl (**2.58**), the catalytic tosylation only provides 19% yield and 60% *ee*. When geminal isopropyl groups are used (**2.59**), no conversion is observed. It seems that the large geminal groups block the formation of the catalyst-substrate complex due to steric hindrance.

Introducing substituents vicinal to the hydroxyl groups (**2.60**) leads to a sharp drop in product *ee*, as well as conversion.

cis-meso-1,2,3-Triols

Dr. Zhen You from the Snapper group previously reported the catalytic enantioselective silylation of triols. It is worthy mentioning that the enantioselectivity of triol silylation is significantly higher than that of diol silylation. Dr. Zhen reported up to >98% *ee* of mono-silylates when using triol substrates and catalyst **2.1**. Two possible reasons account for the very good enantioselectivity. First, a triol has three hydroxyl groups, which can form up to three hydrogen bonds with the catalyst. The stronger interaction leads to better desymmetrization of the alcohol (Figure 10). Second, it was found that the mono-silylation product of a triol can undergo catalytic kinetic resolution, which selectively converts

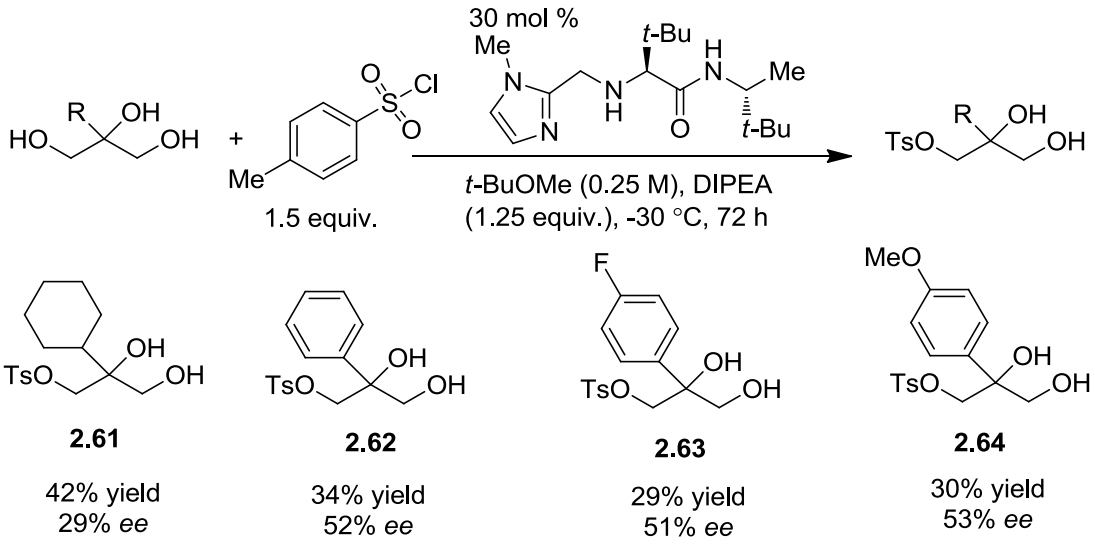
Figure 10



the undesired mono-silylate enantiomer into a bis-silylate product. Hence, the enantiopurity of the mono-silylate product is improved. Based on the research on catalytic enantioselective silylation, catalytic enantioselective tosylation of acyclic and cyclic triols was developed.

Acyclic *meso*-1,2,3-Triols

Scheme 2.15. Acyclic *meso*-1,2,3-Triol Scope of Catalytic Enantioselective Tosylation



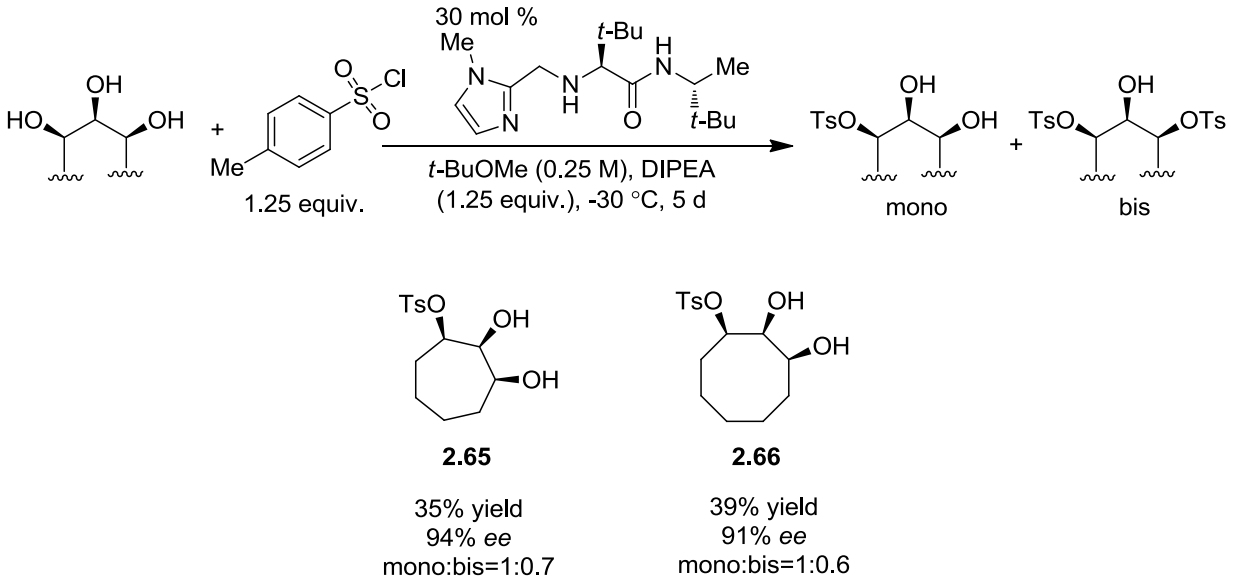
Scheme 2.15 shows that the overall results for acyclic triols are not as good as predicted. When triol **2.61** was used in the catalytic enantioselective tosylation, only 29% *ee* of mono-tosylate was observed. For all of the acyclic *meso*-1,2,3-triol substrates, 1,3-bis-tosylate was found to be the main product of the reaction. The poorer solubility of the triols compared to that of the mono-tosylate products in *t*-BuOMe is most likely the cause of bis-tosylate being the major product. Aromatic substituted acyclic triols were examined for an electronic effect (**2.62**, **2.63** and **2.64**). The results show that in the catalytic enantioselective tosylation of acyclic *meso*-1,2,3-triols, the electron-donating and electron-withdrawing groups on the benzene substituent do not affect the catalytic process much. Substrates **2.62**, **2.63** and **2.64** gave similar

enantioselectivities and mono-tosylate yields. Due to bis-tosylate being the major product, the application of this methodology to acyclic triols is limited.

Cyclic *cis*-*meso*-1,2,3-Triols

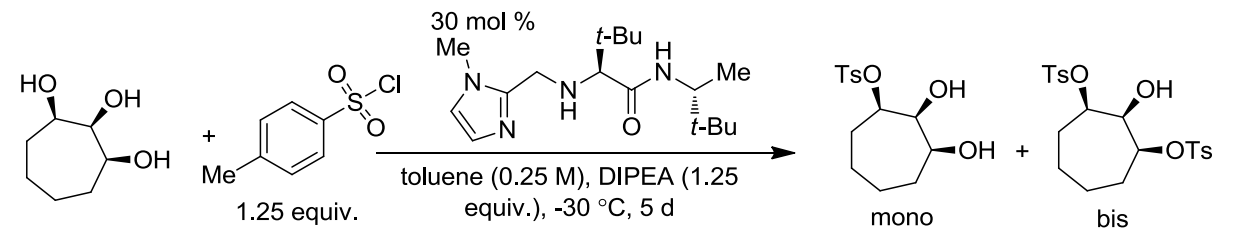
Due to the difficulty of preparing cyclic *cis*-*meso*-1,2,3-triols, only substrates **2.65** and **2.66** were synthesized and their optimal reaction conditions found (Scheme 2.16).

Scheme 2.16. Cyclic *cis*-*meso*-1,2,3-Triol Scope of Catalytic Enantioselective Tosylation



Both triol substrates showed good enantioselectivities, which could be derived from secondary kinetic resolutions of their mono-tosylates. A solvent screen including THF, toluene and *t*-BuOMe showed that *t*-BuOMe is the best solvent (Table 2.9).

Table 2.9. Solvent Screen of Cyclic Triols



Entry	Solvent	Conversion (%)	*ee* (%)	mono/bis
1	*t*-BuOMe	60	94	1:0.7
2	toluene	33	93	1:1.3
3	THF	30	67	1:0.3

The catalytic enantioselective tosylation of **2.65** provided 35% yield and 94% *ee*. Similar to acyclic triols, due to high polarity, **2.65** dissolved poorly in most commonly used solvents and afforded a low mono/bis ratio. Triol **2.66** was synthesized to improve the poor solubility since it has one more methylene in the backbone. Unfortunately, it was still quite insoluble in *t*-BuOMe and led to 39% yield and 91% *ee*, with a low mono/bis product ratio.

2.6 Summary

Selective tosylation of a single hydroxyl group in a molecule containing mutiple hydroxyl groups has been a long-standing challenge in synthetic organic chemistry. A catalytic enantioselective tosylation of alcohols was developed in our group by applying a single-amino-acid-based organocatalyst. The optimal catalyst can be prepared easily in five steps and one purification step with high yield. Also, the catalyst is air and moisture stable. The substrate scope includes *meso*-1,2-diols, *meso*-1,3-diols and *meso*-1,2,3-triols., The catalyst, however, still suffers from low catalytic reactivity, low turnover and enantioselectivity issues, which require 30 mol % catalyst loading, -30 ℃ reaction temperature and days of reaction time to achieve proper results. Development of a more efficient and convenient catalytic enantioselective sulfonylation which can be applied to a broad scope of alcohols is still needed.

2.7 Experimental and Supporting Information

General Information

Infrared (**IR**) spectra were recorded on a Perkin Elmer 781 spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). **^{1}H NMR** spectra were recorded on a Varian GN-400 (400 MHz) and a Varian Inova-500 (500 MHz). Chemical shifts are reported in ppm with the solvent reference as the internal standard ($CHCl_3$: δ 7.26). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), and coupling constants (Hz). **^{13}C NMR** spectra were recorded on a Varian GN-400 (100 MHz) and a Varian Inova-500 (125 MHz) with complete proton coupling. Chemical shifts are reported in ppm with the solvent reference as the internal standard ($CHCl_3$: δ 77.23). Melting points (**MP**) were taken with a Laboratory Device Melt-Temp and were uncorrected. **Enantiomeric ratios** were determined by analytical liquid chromatography (HPLC) Shimadzu chromatograph (Chiral Technologies Chiralpak OD (4.6 x 250 mm)). **Optical rotations** were measured on a Rudolph Research Analytical Autopol IV Automatic Polarimeter. High resolution mass spectrometry (**HRMS**) was performed at the mass spectrometry facility at Boston College.

All reactions were conducted under an open atmosphere in 10 x 75 mm test tubes. All commercially available reagents other than tosyl chloride (TsCl) were used directly for the reaction without any further purification. Liquid reagents were handled with a Gilson Pipetman. Solvents other than *tert*-butylmethyl ether (*t*-BuOMe) were dried on alumina columns using a solvent dispensing system. Tosyl chloride was purchased from Aldrich and was purified from $CHCl_3$/Hexane (1:5). *tert*-Butylmethyl ether was purchased from Aldrich and was used without distillation. Amino acids, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and

hydroxybenzotriazole (HOBt) were purchased from Advanced Chem Tech; 1-methyl-2-imidazolecarboxaldehyde, 4M hydrogen chloride in 1,4-dioxane and diisopropylethylamine (DIPEA) were purchased from Aldrich. *cis*-4-Cyclopenten-1,3-diol was purchased from Fluka. *cis*-Cyclopentane-1,2-diol, *cis*-cyclohexane-1,2-diol, *cis*-cyclooctane-1,2-diol and *meso*-butane-2,3-diol were purchased from Aldrich. *cis*-Cyclohex-4-ene-1,2-diol, *cis*-cyclooct-5-ene-1,2-diol and *cis*-cycloheptane-1,2-diol were prepared from their corresponding alkenes.[footage a note]

General Procedure of Enantioselective Tosylation of meso-1,2-diols and meso-triols

Catalyst **2.1** (9.0 mg, 0.030 mmol) and *meso*-alcohol (0.10 mmol) were weighed into a 10 x 75 mm test tube with a stir bar. *t*BuOMe (180 μL) and DIPEA (22 μL, 0.125 mmol) were added into the test tube with a pipetman. The test tube was capped with a septum and the mixture was allowed to stir at room temperature for 10 min to allow the contents to dissolve. Then, the mixture was cooled to -78 ℃. A solution of *p*-TsCl (24.0 mg, 0.125 mmol) in *t*BuOMe (200 μL) was added to the reaction mixture with a pipetman. The test tube was capped with a septum and wrapped with Teflon tape. The mixture was allowed to sir in a cryocool at -30 ℃ for the reported period of time. Then the reaction was quenched by adding 20 drops of MeOH at -30 ℃. The mixture was allowed to warm to room temperature, and then was purified by silica gel chromatography.

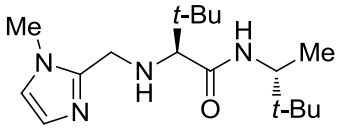
General Procedure of Enantioselective Tosylation of meso-1,3-diols

Catalyst **2.1** (9.0 mg, 0.030 mmol) and *meso*-alcohol (0.10 mmol) were weighed into a 10 x 75 mm test tube with a stir bar. Toluene (180 μL) and DIPEA (22 μL, 0.125 mmol) were added into the test tube with a pipetman. The test tube was capped with a septum and the mixture was allowed to stir at room temperature for 10 min in order to allow the contents to dissolve. Then, the mixture was cooled to -78 ℃. A solution of *p*-TsCl (24.0 mg, 0.125 mmol) in toluene (200

μL) was added to the reaction mixture with a pipetman. The test tube was capped with a septum and wrapped with Teflon tape. The mixture was allowed to sir in a cryocool at -30 ℃ for the reported period of time. Then the reaction was quenched by adding 20 drops of MeOH at -30 ℃. The mixture was allowed to warm to room temperature, and then was purified by silica gel chromatography.

Procedure of Preparing Catalyst

(*S*)-N-((*R*)-3,3-dimethylbutan-2-yl)-3,3-dimethyl-2-((1-methyl-1H-imidazol-2-yl)methylamino)butanamide:



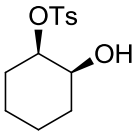
2.1

tert-Leucine (2.0 g, 10 mmol) was dissolved in 15 mL of a 2 M NaOH solution that was at 0 ℃. Di-*tert*-butyl dicarbonate (3.9 g, 12 mmol) was slowly added. The solution was allowed to warm to room temperature and allowed to stir for a further 2 h. The mixture was then acidified to pH 2 by adding concentrated HCl and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo, resulting in a white solid. The solid and (*R*)-3,3-dimethyl-2-butylamine (1.3 mL, 10 mmol) were dissolved in 40 mL of CH_2Cl_2. To this solution, EDC (2.1 g, 11 mmol), HOBt (1.7 g, 11 mmol) and DIPEA (4.4 mL, 25 mmol) were added. The solution was allowed to stir at room temperature for 12 h, and then 20 mL of 1 M HCl were added. The organic layer was separated and washed with a saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo to afford a white solid. The white solid was placed in a flask and 7.5 mL of 4 M HCl in dioxane were added. The mixture was allowed to stir at room temperature for 1 h. To the mixture, water (40 mL) was added. The aqueous layer was washed with CH_2Cl_2 and basified to pH 12 by adding 1 M NaOH solution. The resulting solution was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were

combined, washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting white solid was dissolved in of CH_2Cl_2 (5 mL). 1-methyl-2-imidazolecarboxaldehyde (1.1 g, 10 mmol) and 1.0 g anhydrous $MgSO_4$ were added and the solution was allowed to stir at room temperature under nitrogen atmosphere. The solution was filtered and concentrated in vacuo. The remaining solid was dissolved in of MeOH (10 mL). The solution was cooled to 0 ℃, followed by the addition of by adding $NaBH_4$ (1.1 g, 30 mmol). The mixture was allowed to stir for 0.5 h at 0 ℃ and a 1 h further at room temperature. Then a saturated solution of $NaHCO_3$ (5 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography (97:3 CH_2Cl_2/MeOH).

Characterization Data

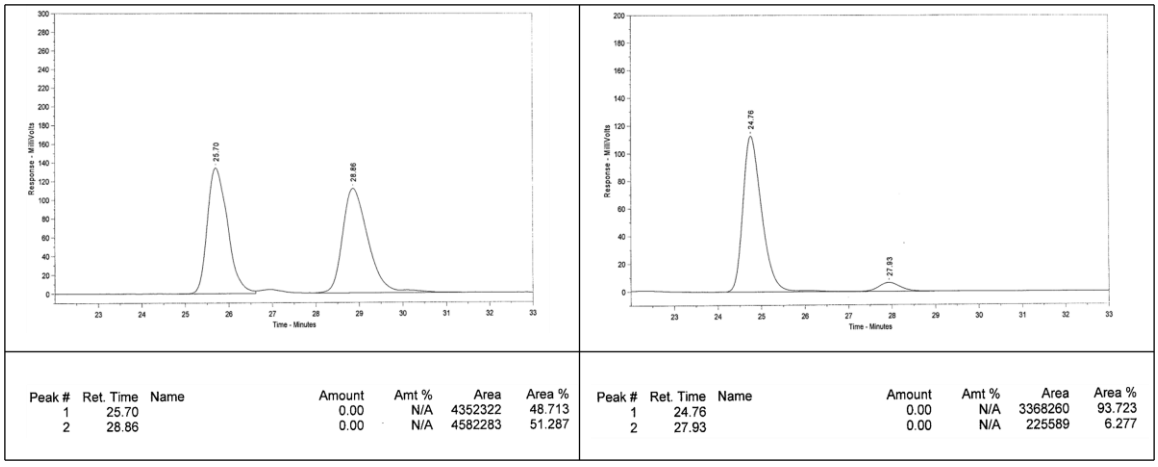
(1*R*,2*S*)-2-hydroxycyclohexyl 4-methylbenzenesulfonate:



2.2

^{1}H NMR ($CDCl_3$, 400 MHz): 7.81 (2H, d, *J* = 8.4 Hz), 7.34 (2H, d, *J* = 8.4 Hz), 4.63 (1H, m), 3.82 (1H, m), 2.45 (3H, s), 1.98 (1H, d, *J* = 5.2 Hz), 1.91 (1H, m), 1.73 (1H, m), 1.63-1.44 (4H, m), 1.32-1.25 (2H, m). **^{13}C NMR** ($CDCl_3$, 100 MHz): 145.0, 134.4, 130.1, 127.9, 83.4, 69.2, 30.5, 28.0, 22.0, 21.9, 21.0. **Optical Rotation**: $[\alpha]^{20}_{D}$ 6.4 (*c* = 1.0, $CHCl_3$).

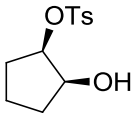
Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm x 0.46 cm), 90:10 hexane/*i*-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 87% *ee* sample:



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	25.70		0.00	N/A	4352322	48.713
2	28.86		0.00	N/A	4582283	51.287

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	24.76		0.00	N/A	3368260	93.723
2	27.93		0.00	N/A	225589	6.277

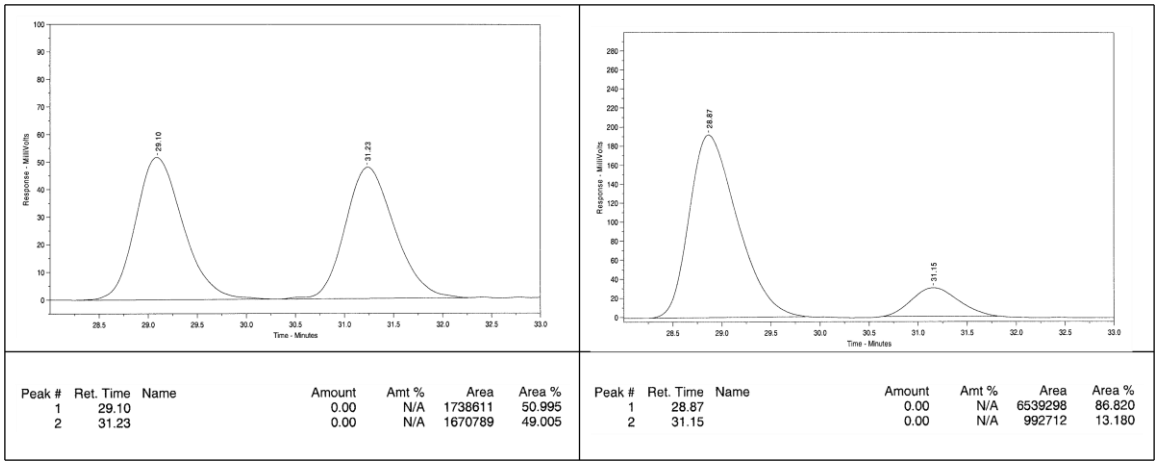
(1*R*,2*S*)-2-hydroxycyclopentyl 4-methylbenzenesulfonate:



2.44

^{1}H NMR ($CDCl_3$, 400 MHz): 7.81 (2H, d, *J* = 8.4 Hz), 7.34 (2H, d, *J* = 8.4 Hz), 4.66 (1H, m), 4.12 (1H, m), 2.45 (3H, s), 2.16 (1H, br), 1.89-1.77 (4H, m), 1.74-1.66 (1H, m), 1.56-1.45 (1H, m). **^{13}C NMR** ($CDCl_3$, 100 MHz): 145.2, 133.9, 130.1, 128.0, 84.4, 73.0, 30.2, 28.1, 21.9, 19.1. **Optical Rotation**: $[\alpha]^{20}_{D}$ 4.5 (*c* = 1.0, $CHCl_3$).

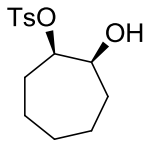
Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm x 0.46 cm), 90:10 hexane/*i*-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 74% *ee* sample:



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	29.10		0.00	N/A	1738611	50.995
2	31.23		0.00	N/A	1670789	49.005

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	28.87		0.00	N/A	6539298	86.820
2	31.15		0.00	N/A	992712	13.180

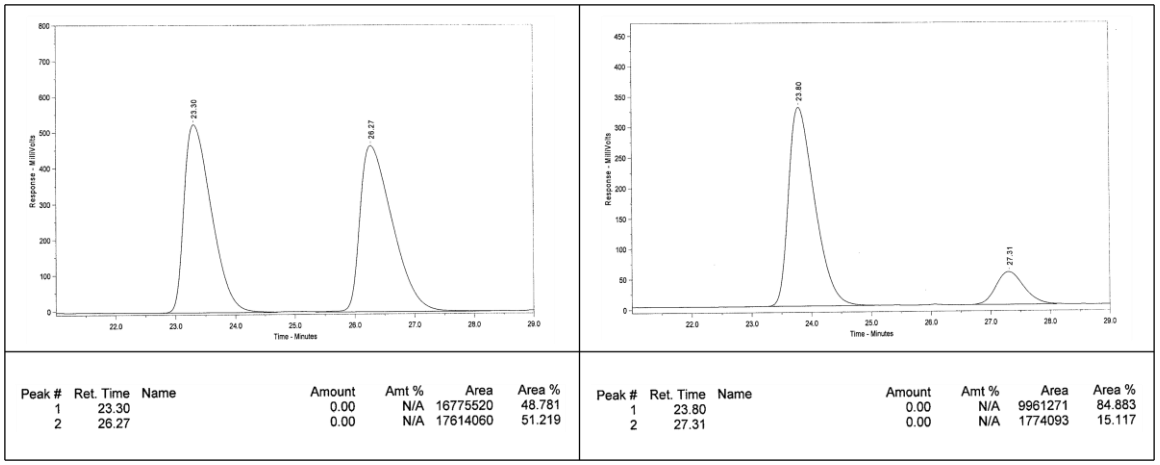
(1*R*,2*S*)-2-hydroxycycloheptyl 4-methylbenzenesulfonate:



2.45

IR (neat, thin film): 3534 (br), 2931 (w), 2864 (w), 1458 (w), 1351 (m), 1172 (s), 1096 (m), 903 (s), 868 (m), 814 (m), 670 (s), 555 (m) cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz): 7.77 (2H, d, *J* = 8.4 Hz), 7.30 (2H, d, *J* = 8.4 Hz), 4.64 (1H, dt, *J* = 8.8, 2.6 Hz), 3.90 (1H, dt, *J* = 8.0, 2.8 Hz), 2.41 (3H, s), 2.11 (1H, s), 1.92 (1H, m), 1.77-1.25 (9H, m). **^{13}C NMR** ($CDCl_3$, 100 MHz): 145.0, 130.1, 127.9, 87.0, 72.5, 31.2, 28.8, 26.8, 22.4, 21.8, 21.7. **HRMS** [M^++NH_4]: Calculated for $C_{14}H_{24}N_1O_4S_1$: 302.1426; Found: 302.1434. **Optical Rotation**: $[\alpha]^{20}_D$ 6.4 (*c* = 1.0, $CHCl_3$).

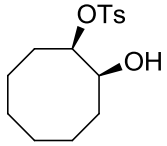
Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm x 0.46 cm), 90:10 hexane/*i*-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 70% *ee* sample:



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	23.30		0.00	N/A	16775520	48.781
2	26.27		0.00	N/A	17614060	51.219

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	23.80		0.00	N/A	9961271	84.883
2	27.31		0.00	N/A	1774093	15.117

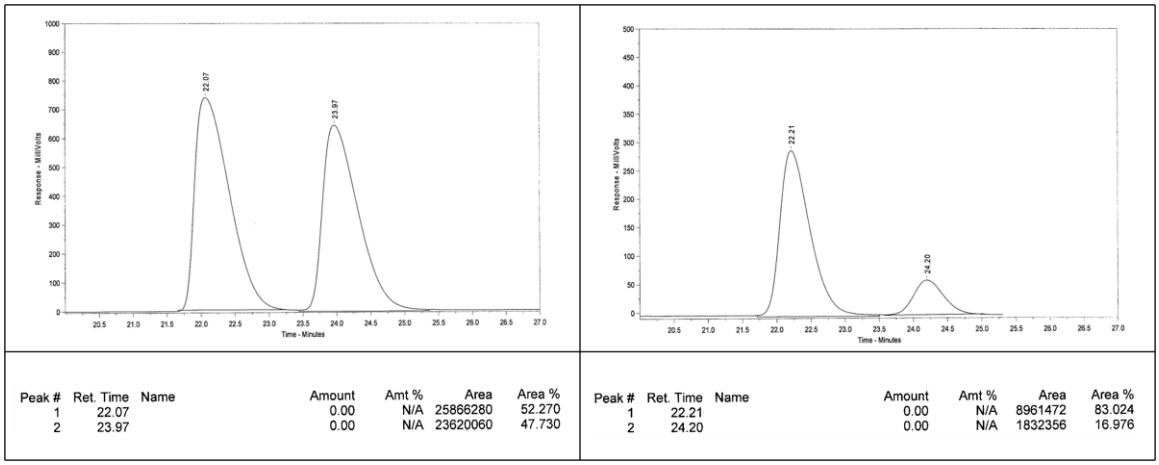
(1*R*,2*S*)-2-hydroxycyclooctyl 4-methylbenzenesulfonate:



2.46

IR (neat, thin film): 3529 (br), 2925 (w), 2860 (w), 1598 (w), 1450 (w), 1188 (w), 1173 (m), 1097 (w), 904 (s), 863 (w), 814 (w), 726 (s), 688 (m), 648 (w), 554 (m) cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz): 7.79 (2H, d, *J* = 8.4 Hz), 7.33 (2H, d, *J* = 8.4 Hz), 4.74 (1H, m), 3.93 (1H, m), 2.43 (3H, s), 2.28 (1H, s), 2.06 (1H, m), 1.76-1.34 (11H, m). **^{13}C NMR** ($CDCl_3$, 100 MHz): 145.0, 134.2, 130.0, 127.9, 86.1, 71.8, 30.3, 28.2, 27.0, 25.6, 24.1, 21.9, 21.8. **HRMS** [M^++H]: Calculated for $C_{15}H_{23}O_4S_1$: 299.1317; Found: 299.1303. **Optical Rotation**: $[\alpha]^{20}_D$ 9.6 (*c* = 1.0, $CHCl_3$).

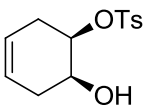
Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm x 0.46 cm), 90:10 hexane/*i*-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 66% *ee* sample:



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	22.07		0.00	N/A	25866280	52.270
2	23.97		0.00	N/A	23620060	47.730

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	22.21		0.00	N/A	8961472	83.024
2	24.20		0.00	N/A	1832356	16.976

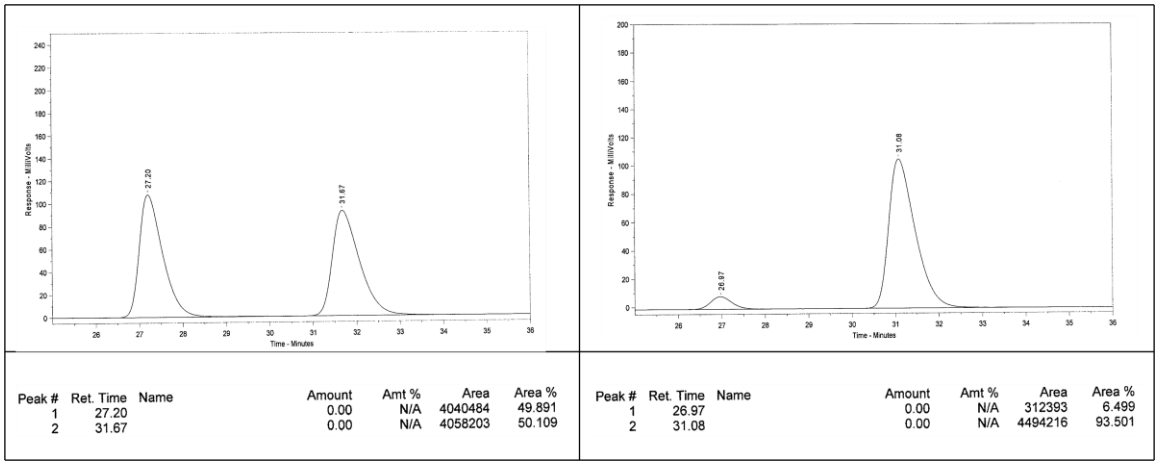
(1*R*,6*S*)-6-hydroxycyclohex-3-en-1-yl 4-methylbenzenesulfonate:



2.47

IR (neat, thin film): 3527 (br), 3034 (w), 2924 (w), 1598 (w), 1350 (m), 1188 (m), 1172 (s), 1096 (m), 1070 (w), 975 (m), 945 (m), 903 (s), 876 (s), 832 (m), 813 (m), 756 (w), 729 (m), 662 (s), 607 (m), 552 (s) cm^{-1}.**^{1}H NMR** ($CDCl_3$, 400 MHz): 7.79 (2H, d, *J* = 8.4 Hz), 7.32 (2H, d, *J* = 8.4 Hz), 5.54 (1H, m), 5.44 (1H, m), 4.73 (1H, m), 4.01 (1H, m), 2.42 (3H, s), 2.37 (1H, s), 2.34-2.16 (4H, m). **^{13}C NMR** ($CDCl_3$, 100 MHz): 145.0, 134.0, 130.0, 127.8, 124.1, 122.5, 80.8, 67.2, 31.5, 28.6, 21.8. **HRMS** [M^++NH_4]: Calculated for $C_{13}H_{20}N_1O_4S_1$: 286.1113; Found: 286.1118. **Optical Rotation**: $[\alpha]^{20}_D$ 11 (*c* = 1.0, $CHCl_3$).

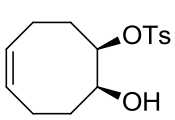
Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm x 0.46 cm), 90:10 hexane/*i*-PrOH, 0.7 mL/min, 220 nm); chromatograms are illustrated below for a 87% *ee* sample:



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	27.20		0.00	N/A	4040484	49.891
2	31.67		0.00	N/A	4058203	50.109

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	26.97		0.00	N/A	312393	6.499
2	31.08		0.00	N/A	4494216	93.501

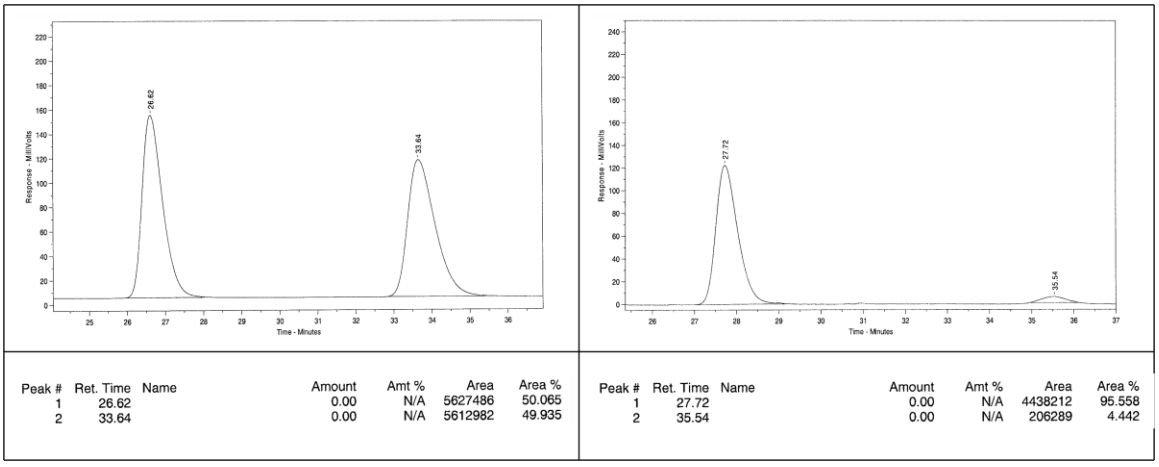
(1*R*,8*S*,*Z*)-8-hydroxycyclooct-4-en-1-yl 4-methylbenzenesulfonate:



2.48

IR (neat, thin film): 3530 (br), 3019 (w), 2939 (w), 1598 (w), 1352 (w), 1188 (w), 1173 (m), 1097 (s), 1033 (w), 902 (s), 873 (m), 837 (w), 813 (w), 725 (s), 670 (m), 648 (w), 573 (w), 555 (m) cm^{-1}.**^{1}H NMR** ($CDCl_3$, 400 MHz): 7.78 (2H, d, *J* = 8.4 Hz), 7.33 (2H, d, *J* = 8.4 Hz), 5.62 (2H, m), 4.77 (1H, m), 4.01 (1H, m), 2.50 (2H, m), 2.43 (3H, s), 2.33 (1H, s), 2.12-1.54 (6H, m). **^{13}C NMR** ($CDCl_3$, 100 MHz): 145.0, 133.9, 130.8, 130.0, 129.3, 127.9, 87.9, 73.6, 33.2, 30.8, 21.9, 21.8, 21.4. **HRMS** [M^++NH_4]: Calculated for $C_{15}H_{24}N_1O_4S_1$: 314.1426; Found: 314.1429. **Optical Rotation**: $[\alpha]^{20}_D$ 32 (*c* = 1.0, $CHCl_3$).

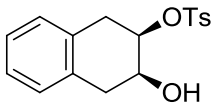
Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm x 0.46 cm), 90:10 hexane/*i*-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 91% *ee* sample:



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	26.62		0.00	N/A	5627486	50.065
2	33.64		0.00	N/A	5612982	49.935

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	27.72		0.00	N/A	4438212	95.558
2	35.54		0.00	N/A	206289	4.442

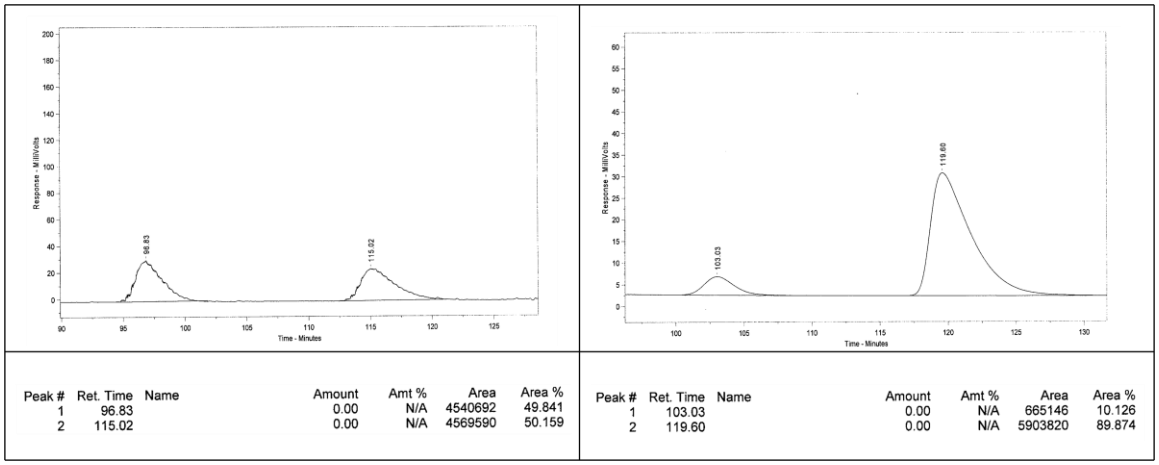
(2*R*,3*S*)-3-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl 4-methylbenzenesulfonate:



2.50

MP: 121.5-122 ℃. **IR** (neat, thin film): 3518 (br), 2971 (w), 2923 (w), 1496 (w), 1348 (m), 1173 (s), 1096 (w), 1072 (w), 956 (w), 910 (m), 820 (w), 750 (w), 761 (w), 667 (w), 555 (m) cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.82 (2H, d, *J* = 8.0 Hz), 7.34 (2H, d, *J* = 8.0 Hz), 7.15-7.6.97 (4H, m), 4.93 (1H, m), 4.23 (1H, m), 3.20-2.93 (4H, m), 2.45 (3H, s), 2.41 (1H, s). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 145.2, 134.0, 132.5, 131.6, 130.1, 129.3, 129.0, 128.0, 126.8, 126.5, 80.9, 67.7, 34.8, 32.1, 21.8. **HRMS** [M^++NH_4]: Calculated for $C_{17}H_{22}N_1O_4S_1$: 336.1270; Found: 336.1285. **Optical Rotation**: $[\alpha]^{20}_D$ -18 (*c* = 1.0, $CHCl_3$).

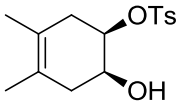
Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm x 0.46 cm), 90:10 hexane/*i*-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 80% *ee* sample:



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	96.83		0.00	N/A	4540692	49.841
2	115.02		0.00	N/A	4569590	50.159

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	103.03		0.00	N/A	665146	10.126
2	119.60		0.00	N/A	5903820	89.874

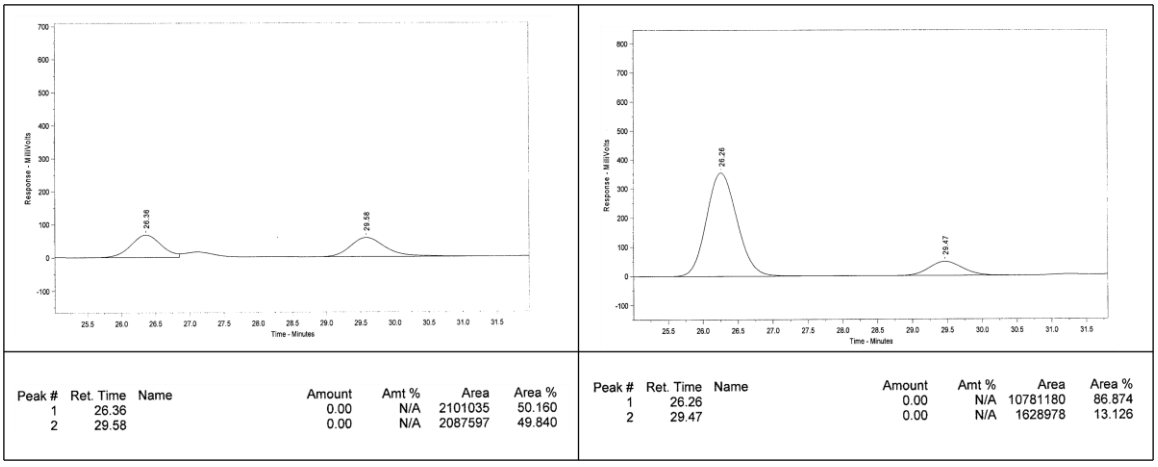
(1*R*,6*S*)-6-hydroxy-3,4-dimethylcyclohex-3-en-1-yl 4-methylbenzenesulfonate:



2.51

IR (neat, thin film): 3533 (br), 2936 (w), 1444 (w), 1353 (m), 1174 (s), 1096 (w), 956 (w), 920 (s), 851 (w), 815 (w), 667 (w), 557 (m) cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.81 (2H, d, *J* = 8.0 Hz), 7.34 (2H, d, *J* = 8.0 Hz), 4.71 (1H, m), 3.98 (1H, m), 2.45 (3H, s), 2.37-2.12 (4H, m), 2.07 (1H, s), 1.58 (3H, s), 1.53 (3H, s). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 145.0, 134.2, 130.1, 127.9, 123.0, 121.7, 81.4, 67.7, 37.6, 34.2, 21.9, 18.8, 18.8. **HRMS** $[M^+ + NH_4]$: Calculated for $C_{15}H_{24}N_1O_4S_1$: 314.1426; Found: 314.1432. **Optical Rotation**: $[\alpha]^{20}_D$ -1.8 (*c* = 1.0, $CHCl_3$).

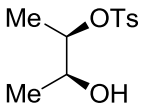
Enantiomeric purity was established by HPLC analysis (Chiralpak AD-H column (25 cm x 0.46 cm), 90:10 hexane/*i*-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 74% *ee* sample:



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	26.36		0.00	N/A	2101035	50.160
2	29.58		0.00	N/A	2087597	49.840

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	26.26		0.00	N/A	10781180	86.874
2	29.47		0.00	N/A	1628978	13.126

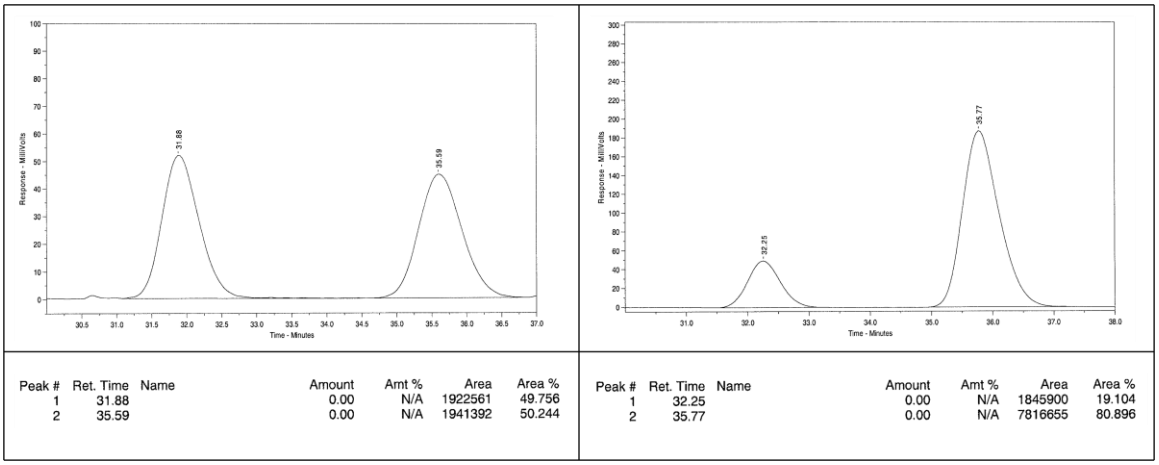
(2*R*,3*S*)-3-hydroxybutan-2-yl 4-methylbenzenesulfonate:



2.52

IR (neat, thin film): 3528 (br), 2985 (w), 1599 (w), 1449 (w), 1352 (w), 1189 (w), 1174 (m), 1099 (w), 1019 (w), 901 (s), 814 (w), 786 (w), 726 (s), 666 (m), 648 (w), 555 (s), 465 (w) cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz): 7.79 (2H, d, *J* = 8.4 Hz), 7.33 (2H, d, *J* = 8.4 Hz), 4.54 (1H, m), 3.86 (1H, m), 2.43 (3H, s), 2.22 (1H, br), 1.19 (3H, d, *J* = 6.4 Hz), 1.09 (3H, d, *J* = 6.4 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): 145.0, 134.2, 130.0, 127.9, 83.4, 69.5, 21.8, 17.8, 15.0. **HRMS** $[M^+ + NH_4]$: Calculated for $C_{11}H_{20}N_1O_4S_1$: 262.1113; Found: 262.1114. **Optical Rotation**: $[\alpha]^{20}_D$ 5.2 (*c* = 1.0, $CHCl_3$).

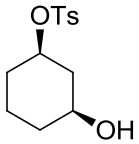
Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm x 0.46 cm), 90:10 hexane/*i*-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 72% *ee* sample:



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	31.88		0.00	N/A	1922561	49.756
2	35.59		0.00	N/A	1941392	50.244

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	32.25		0.00	N/A	1845900	19.104
2	35.77		0.00	N/A	7816655	80.896

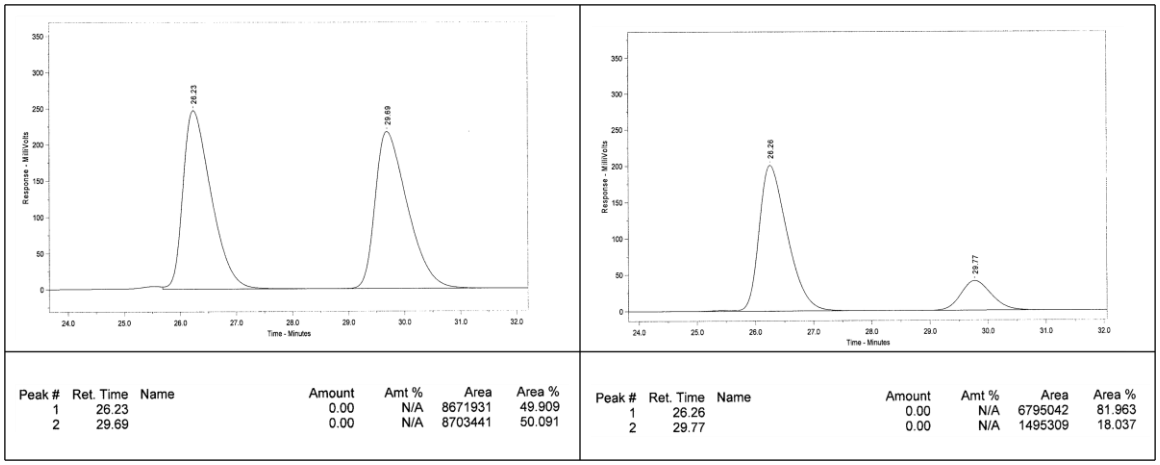
(1*R*,3*S*)-3-hydroxycyclohexyl 4-methylbenzenesulfonate:



2.55

IR (neat, thin film): 3527 (br), 3383 (br), 2943 (w), 2864 (w), 1453 (w), 1352 (m), 1174 (s), 1097 (m), 942 (s), 930 (s), 862 (m), 814 (m), 664 (m), 569 (s), 556 (m) cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.79 (2H, d, *J* = 8.0 Hz), 7.33 (2H, d, *J* = 8.0 Hz), 4.42 (1H, m), 3.58 (1H, m), 2.44 (3H, s), 2.17 (1H, m), 1.90-1.77 (3H, m), 1.68 (1H, br), 1.51-1.17 (4H, m). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 144.8, 134.6, 130.0, 127.8, 79.5, 68.4, 41.5, 34.0, 31.7, 21.8, 19.9. **HRMS** [M^++NH_4]: Calculated for $C_{13}H_{22}N_1O_4S_1$: 288.1270; Found: 288.1269. **Optical Rotation**: $[\alpha]^{20}_D$ 5.9 (*c* = 1.0, $CHCl_3$).

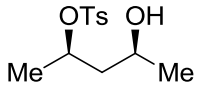
Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm x 0.46 cm), 85:15 hexane/*i*-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 64% *ee* sample:



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	26.23		0.00	N/A	8671931	49.909
2	29.69		0.00	N/A	8703441	50.091

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	26.26		0.00	N/A	6795042	81.963
2	29.77		0.00	N/A	1495309	18.037

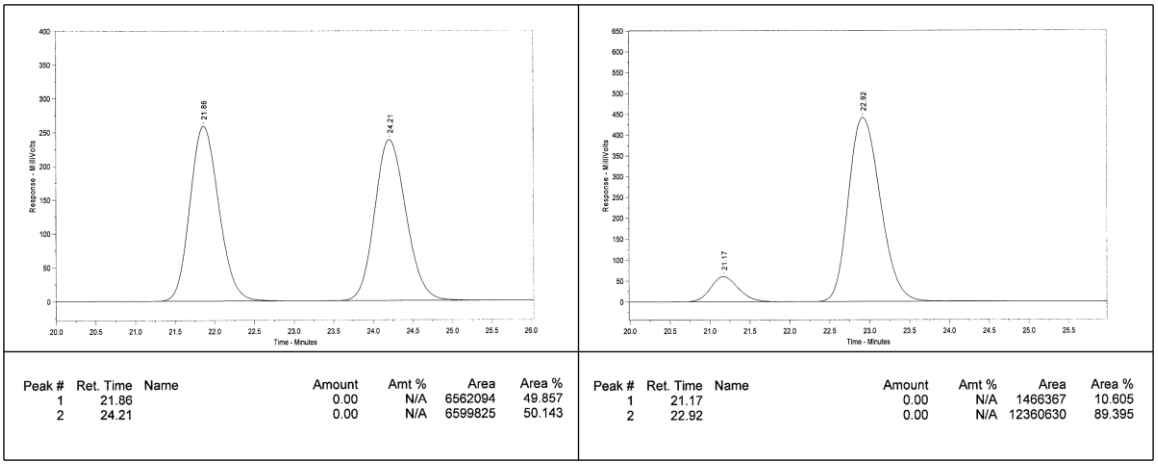
(2*R*,4*S*)-4-hydroxypentan-2-yl 4-methylbenzenesulfonate:



2.57

IR (neat, thin film): 3536 (br), 3399 (br), 2971 (w), 2915 (w), 1352 (m), 1173 (s), 1096 (w), 914 (m), 895 (s), 815 (w), 761 (w), 667 (m), 555 (m) cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.79 (2H, d, *J* = 8.0 Hz), 7.33 (2H, d, *J* = 8.0 Hz), 4.79 (1H, m), 3.82 (1H, m), 2.44 (3H, s), 1.88 (1H, m), 1.71 (1H, br), 1.60 (1H, m), 1.28 (3H, d, *J* = 6.5 Hz), 1.14 (3H, d, *J* = 6.5 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 144.8, 134.5, 130.0, 127.9, 78.7, 65.2, 45.9, 23.9, 21.8, 21.1. **HRMS** [M^++NH_4]: Calculated for $C_{12}H_{22}N_1O_4S_1$: 276.1270; Found: 276.1263. **Optical Rotation**: $[\alpha]^{20}_D$ 11 (*c* = 1.0, $CHCl_3$).

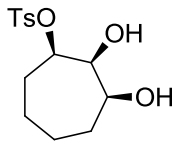
Enantiomeric purity was established by HPLC analysis (Chiralpak AD-H column (25 cm x 0.46 cm), 85:15 hexane/*i*-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 79% *ee* sample:



Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	21.86		0.00	N/A	6562094	49.857
2	24.21		0.00	N/A	6599825	50.143

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	21.17		0.00	N/A	1466367	10.605
2	22.92		0.00	N/A	12360630	89.395

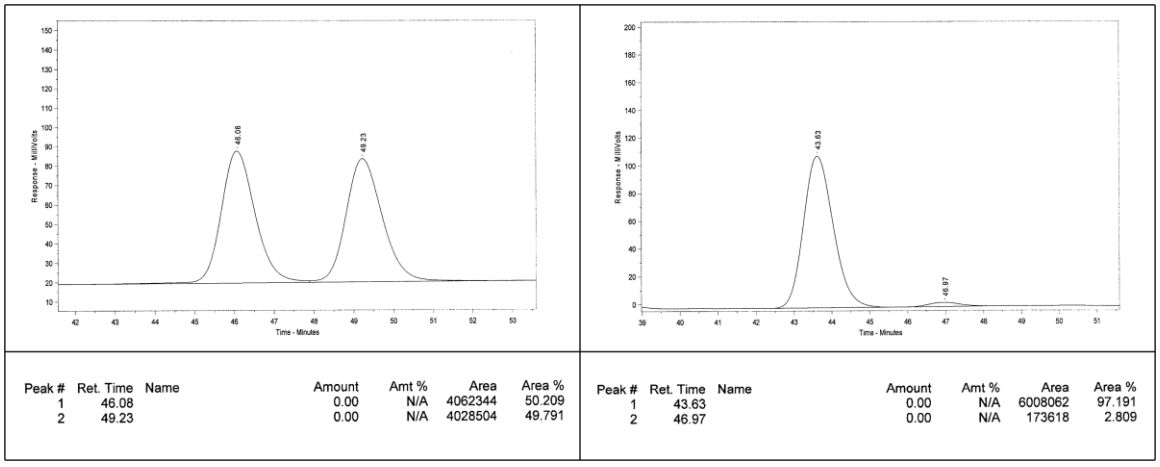
(1*R*,2*S*,3*S*)-2,3-dihydroxycycloheptyl 4-methylbenzenesulfonate:



2.65

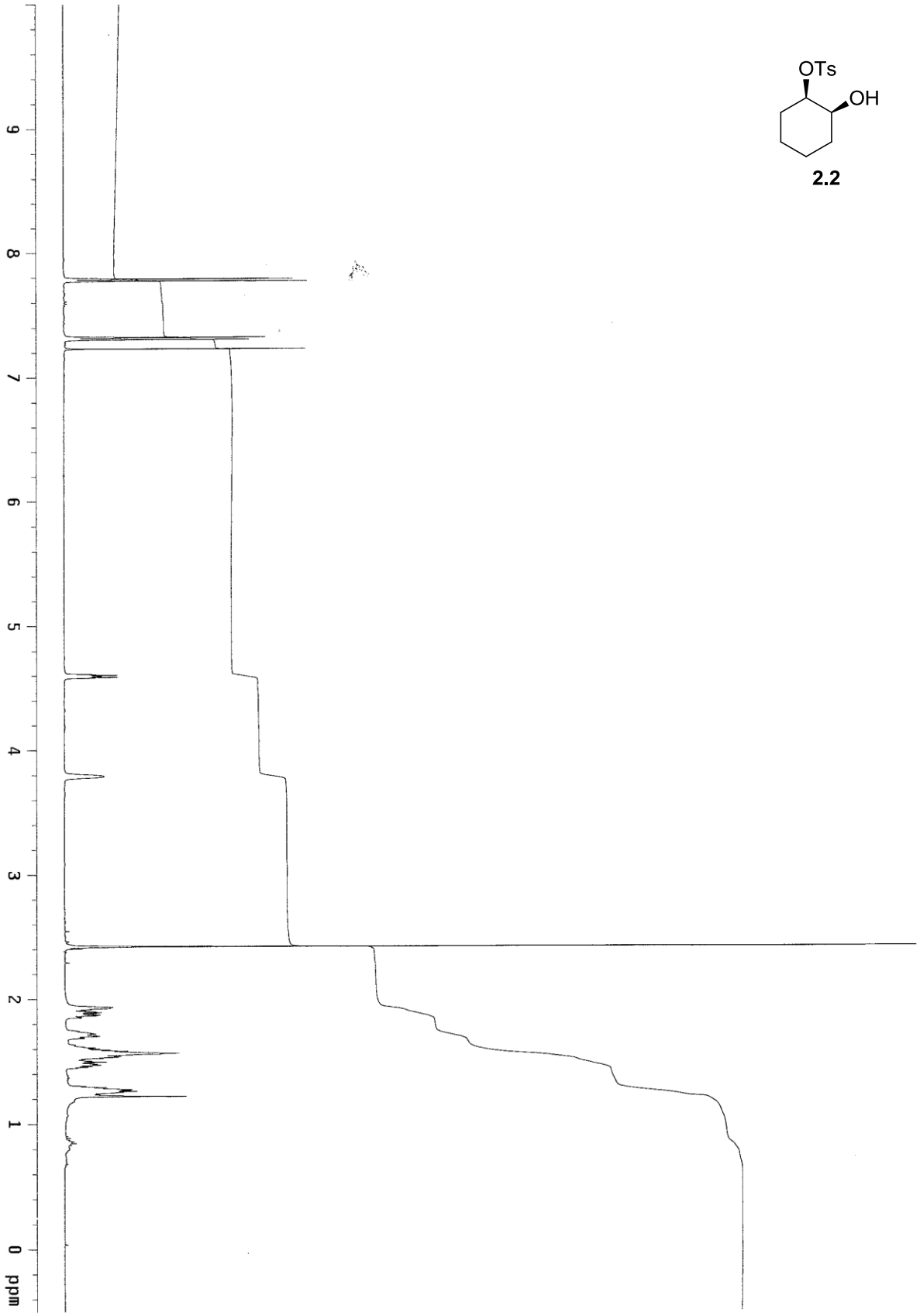
MP: 86.5-87 ℃. **IR** (neat, thin film): 3442 (br), 2936 (w), 2866 (w), 1355 (m), 1173 (s), 1096 (w), 1047 (w), 911 (m), 814 (w), 667 (w), 555 (m) cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.80 (2H, d, *J* = 8.0 Hz), 7.35 (2H, d, *J* = 8.0 Hz), 4.66 (1H, d, *J* = 10.0 Hz), 4.04 (1H, s), 3.73 (1H, m), 2.71 (1H, d, *J* = 4.5 Hz), 2.45 (3H, s), 2.14-2.07 (2H, m), 1.81-1.31 (7H, m). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 145.1, 134.1, 130.1, 127.9, 84.6, 75.6, 71.8, 31.4, 27.8, 23.0, 21.9, 21.6. **HRMS** [M^++NH_4]: Calculated for $C_{14}H_{24}N_1O_5S_1$: 318.1375; Found: 318.1381. **Optical Rotation**: $[\alpha]^{20}_D$ 15 (*c* = 1.0, $CHCl_3$).

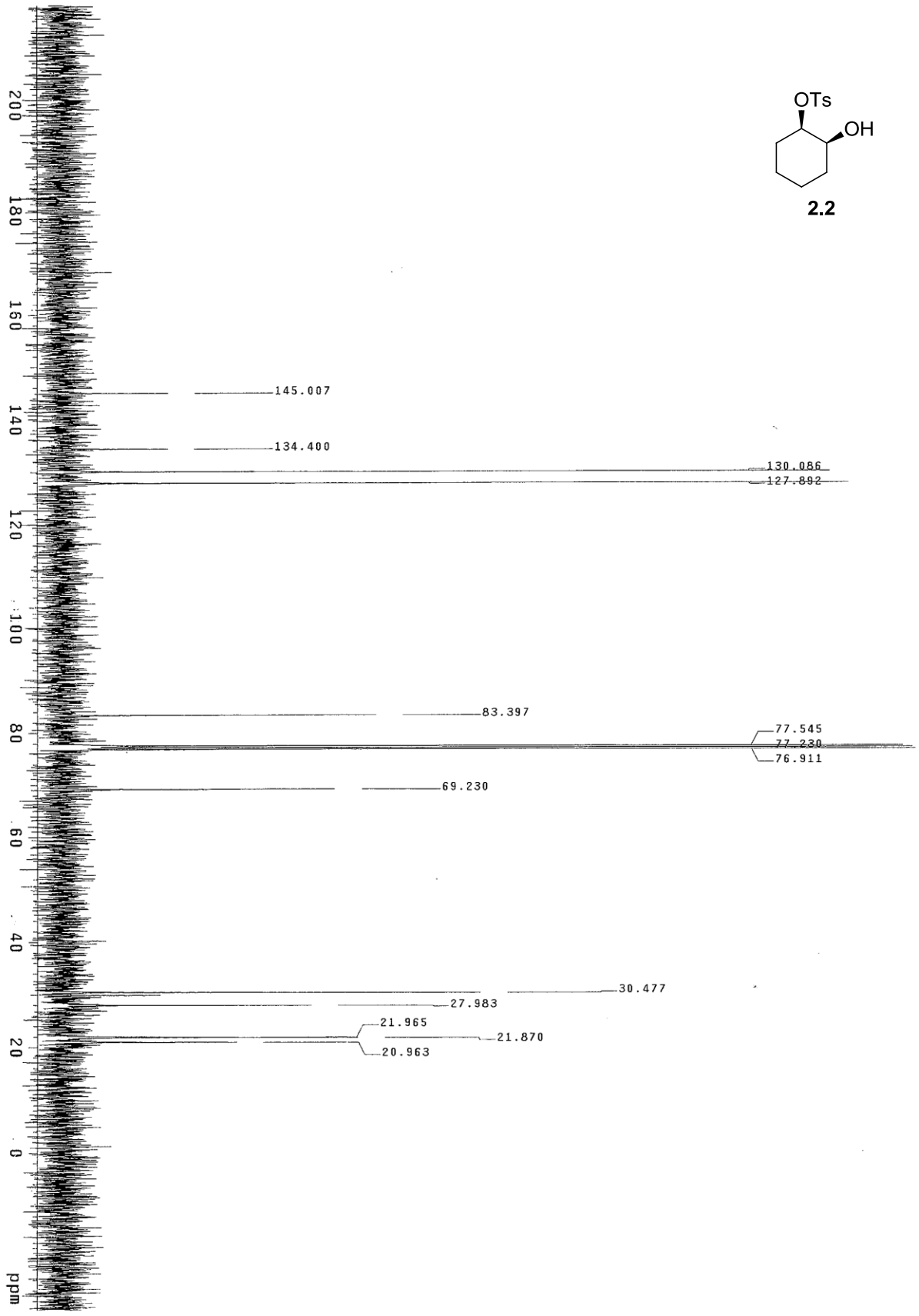
Enantiomeric purity was established by HPLC analysis (Chiralpak AD-H column (25 cm x 0.46 cm), 85:15 hexane/*i*-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 94% *ee* sample:

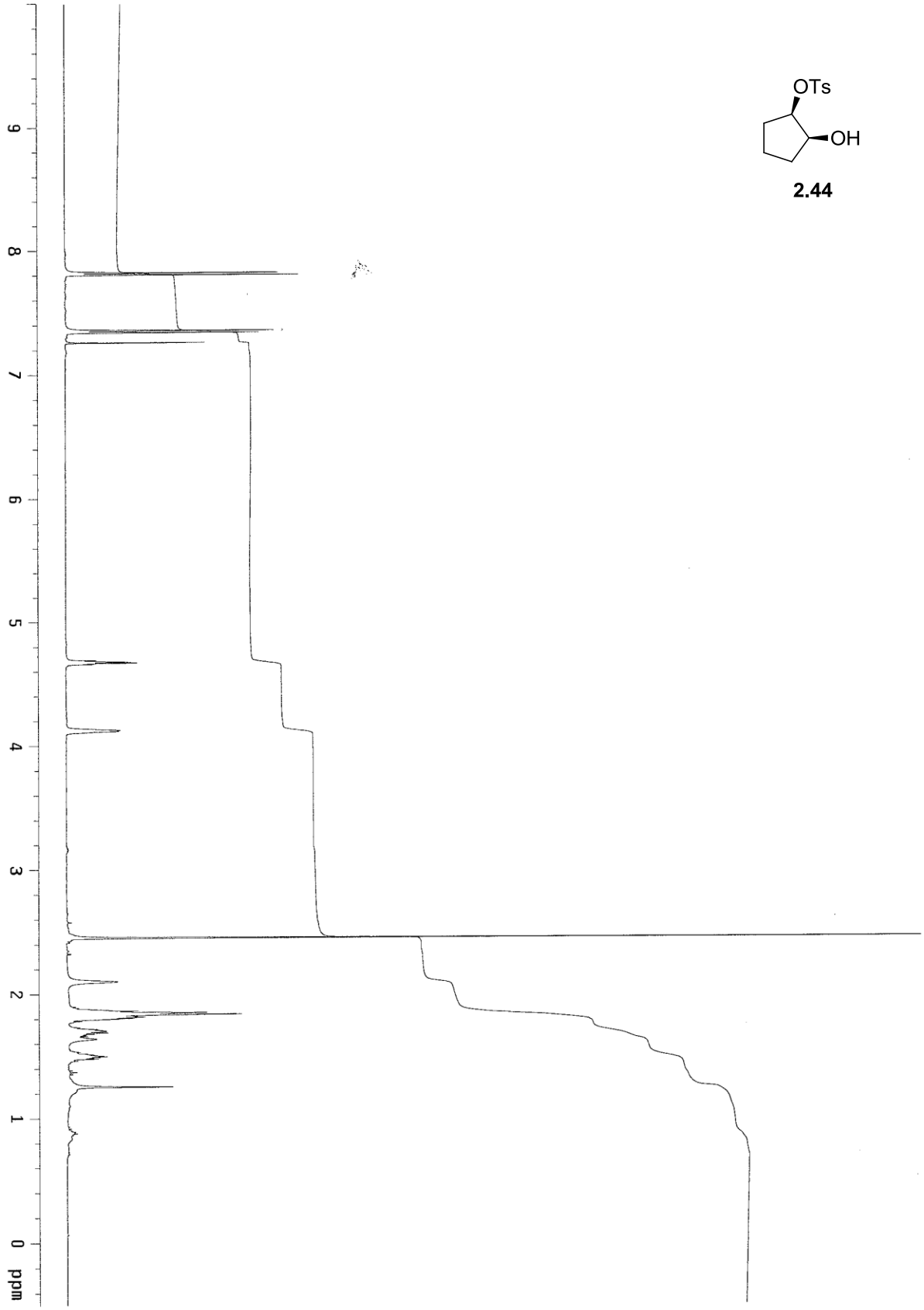


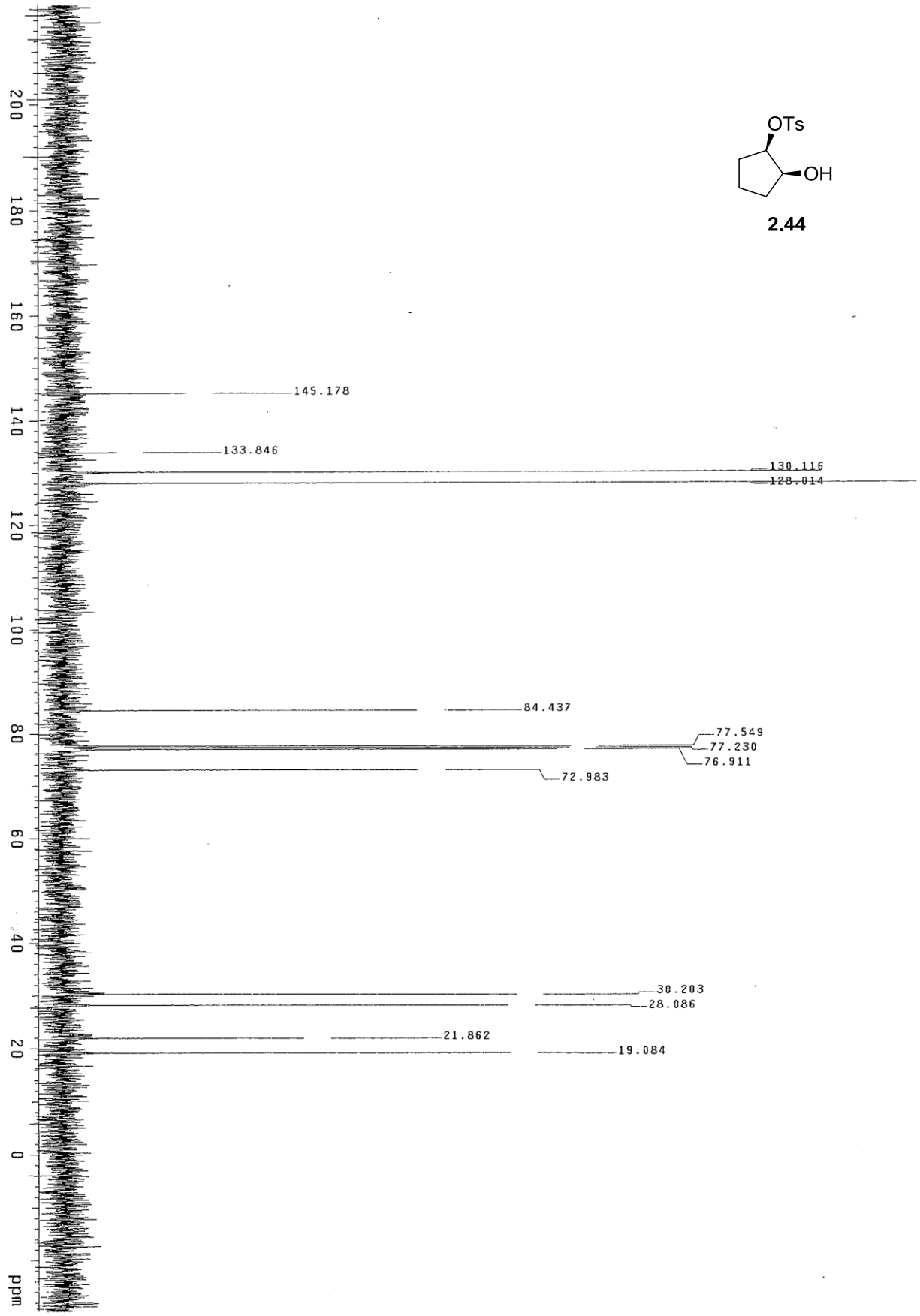
Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	46.08		0.00	N/A	4062344	50.209
2	49.23		0.00	N/A	4028504	49.791

Peak #	Ret. Time	Name	Amount	Amt %	Area	Area %
1	43.63		0.00	N/A	6008062	97.191
2	46.97		0.00	N/A	173618	2.809


OTs
OH
2.2
9
8
7
6
5
4
3
2
1
0
ppm


OTs
OH
2.2
145.007
134.400
130.086
127.892
83.397
77.545
77.230
76.911
69.230
30.477
27.983
21.965
21.870
20.963
200
180
160
140
120
100
80
60
40
20
0
ppm


OTs
OH
2.44
9
8
7
6
5
4
3
2
1
0
ppm


OTs
OH
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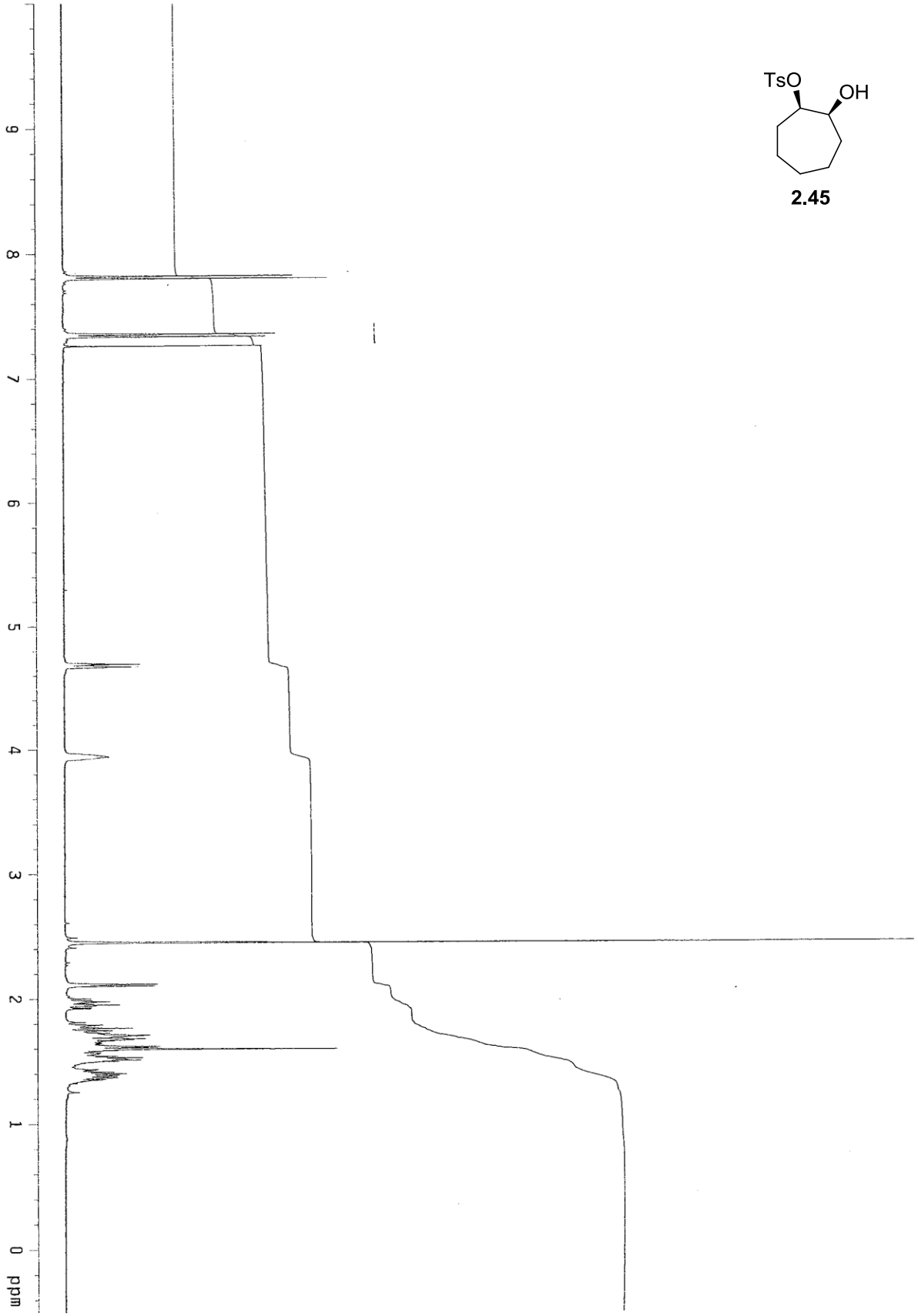
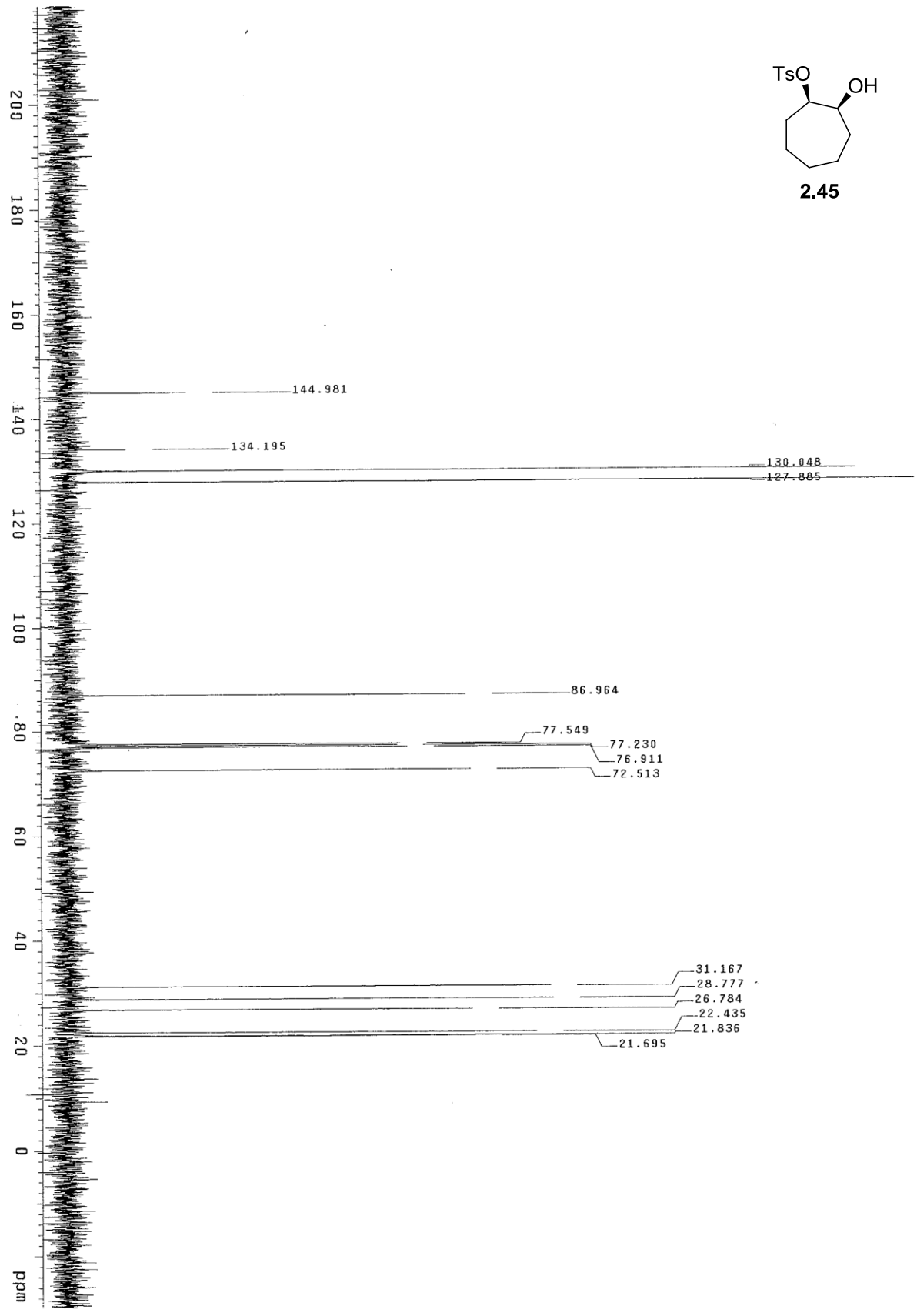
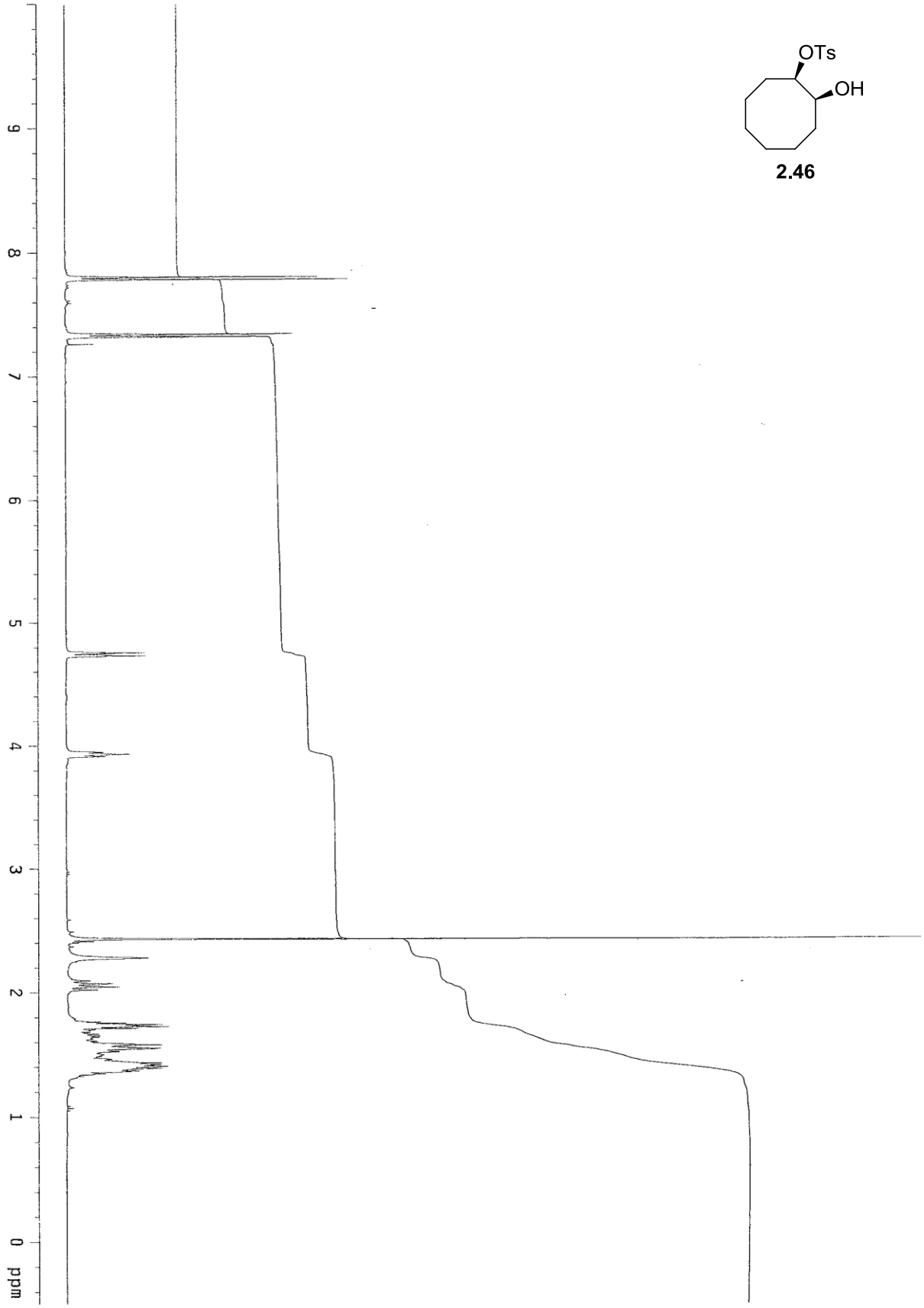
133.846
130.116
128.014
84.437
77.549
77.230
76.911
72.983
30.203
28.086
21.862
19.084
200
180
160
140
120
100
80
60
40
20
0
ppm


TsO
OH
2.45
9
8
7
6
5
4
3
2
1
0 ppm


TsO
OH
2.45
144.981
134.195
130.048
127.885
86.964
77.549
77.230
76.911
72.513
31.167
28.777
26.784
22.435
21.836
21.695
200
180
160
140
120
100
80
60
40
20
0
ppm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OH
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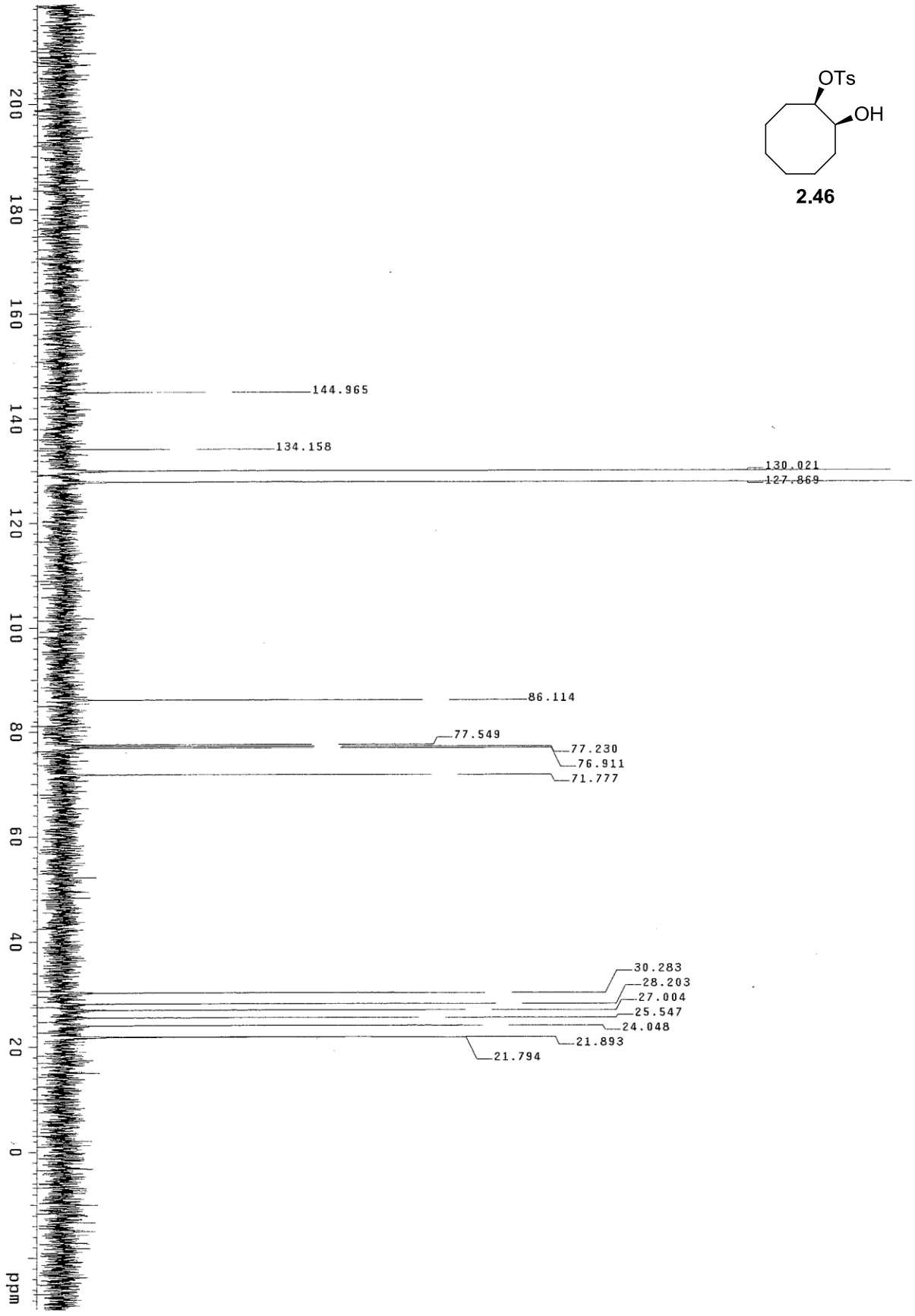
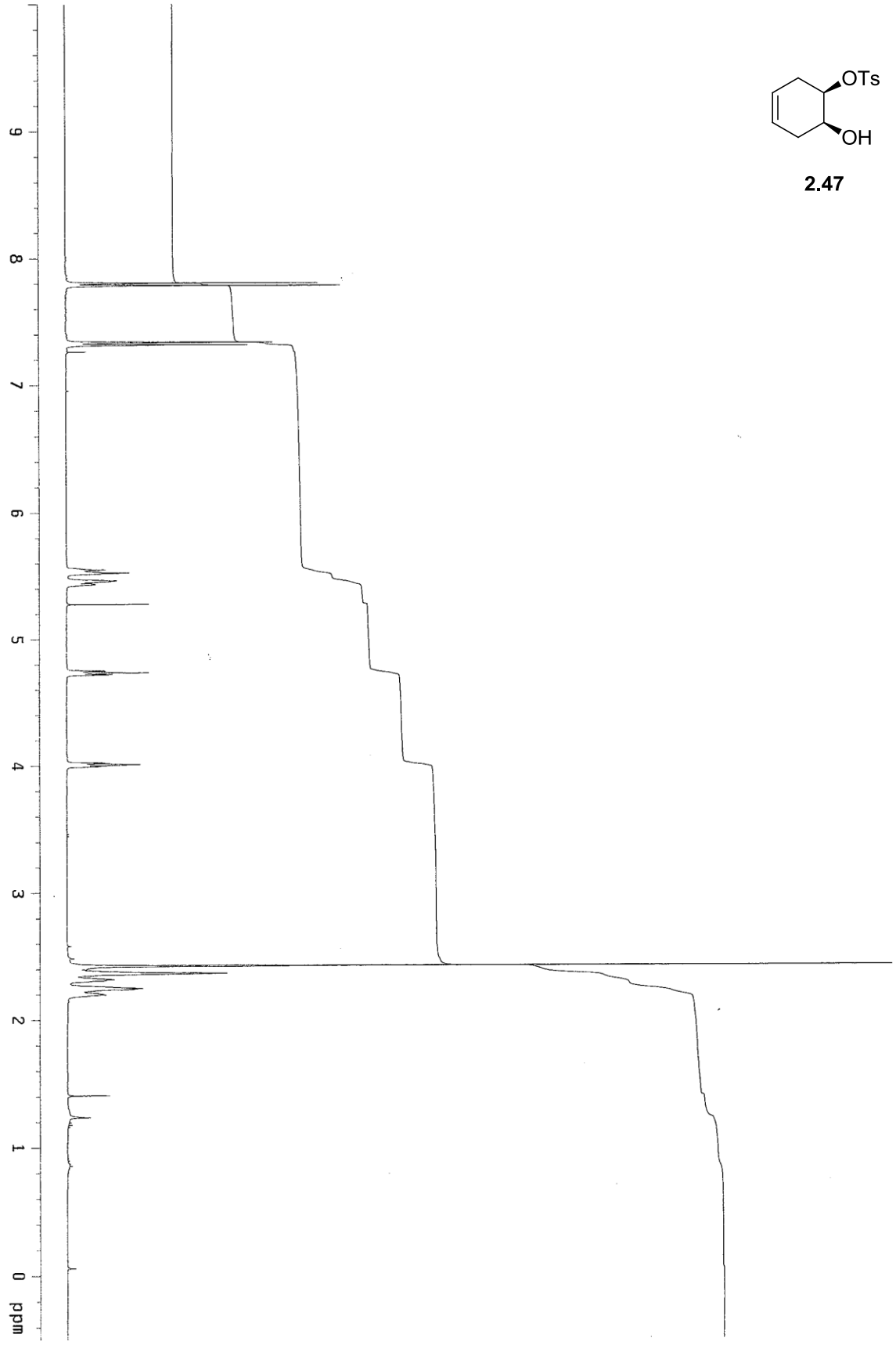
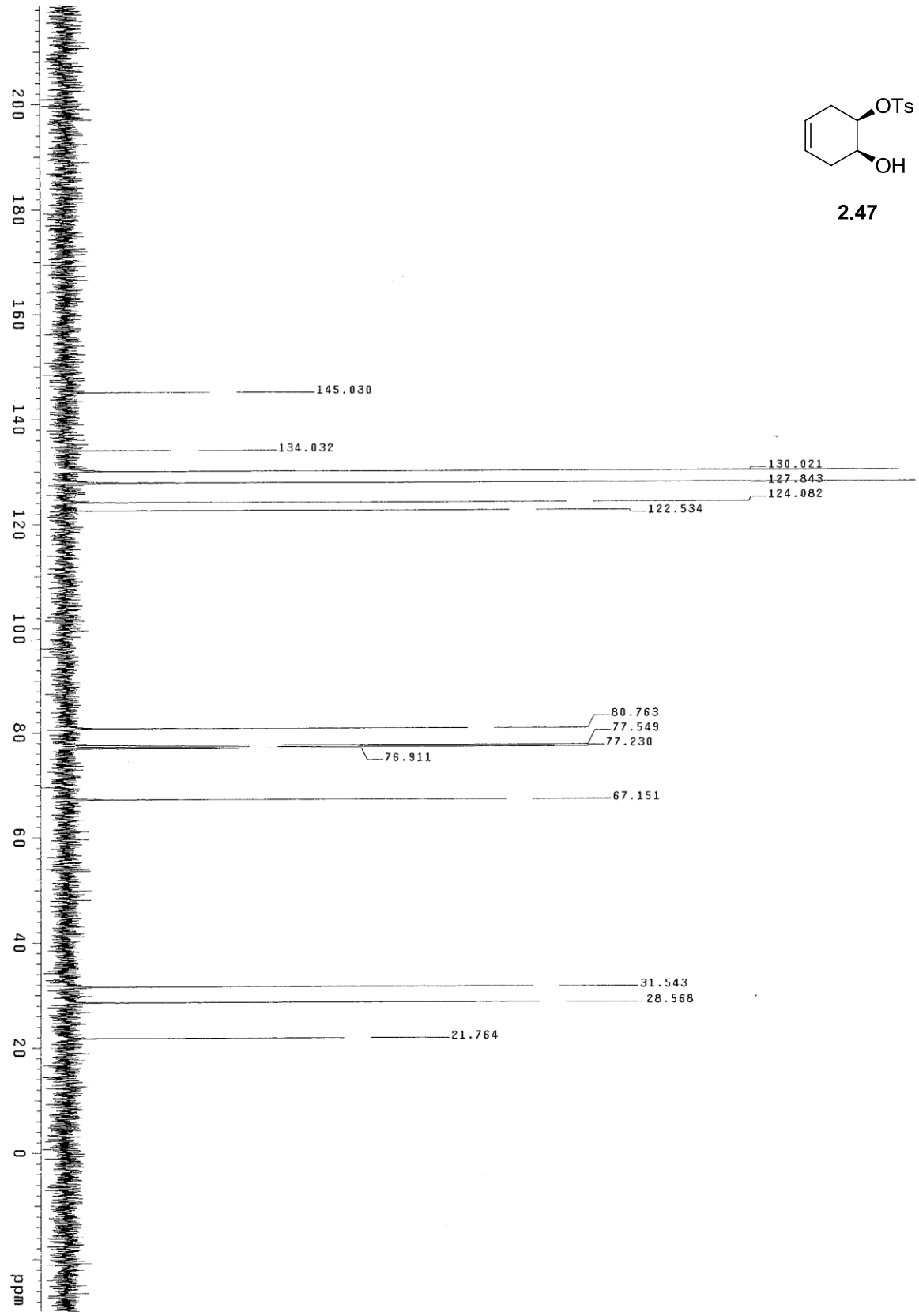
9
8
7
6
5
4
3
2
1
0
ppm

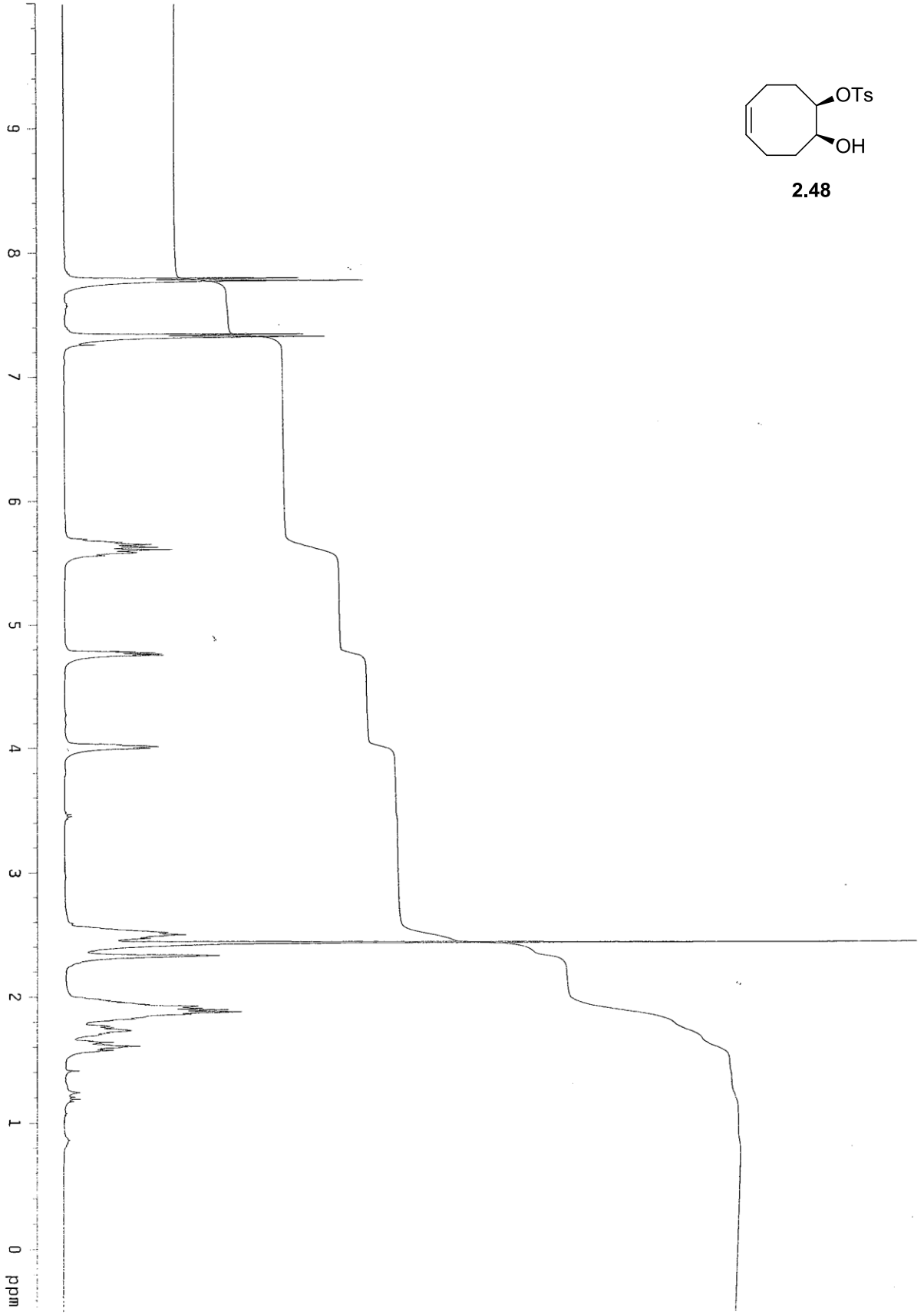

OTs
OH
2.46
144.965
134.158
130.021
127.869
86.114
77.549
77.230
76.911
71.777
30.283
28.203
27.004
25.547
24.048
21.893
21.794
200
180
160
140
120
100
80
60
40
20
0
ppm

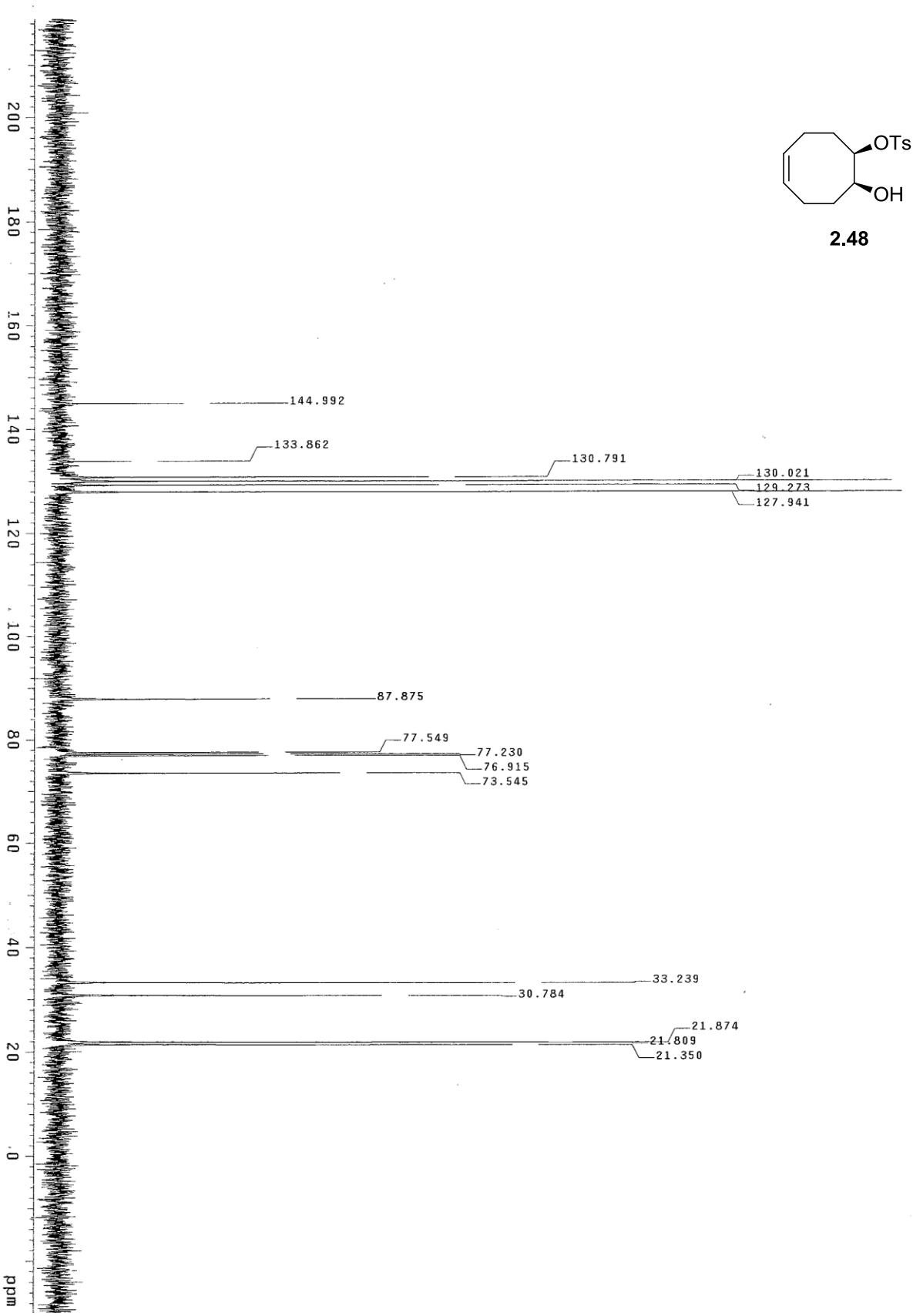

OTs
OH
2.47
9
8
7
6
5
4
3
2
1
0
ppm


145.030
134.032
130.021
127.843
124.082
122.534
80.763
77.549
77.230
76.911
67.151
31.543
28.568
21.764
200
180
160
140
120
100
80
60
40
20
0
ppm

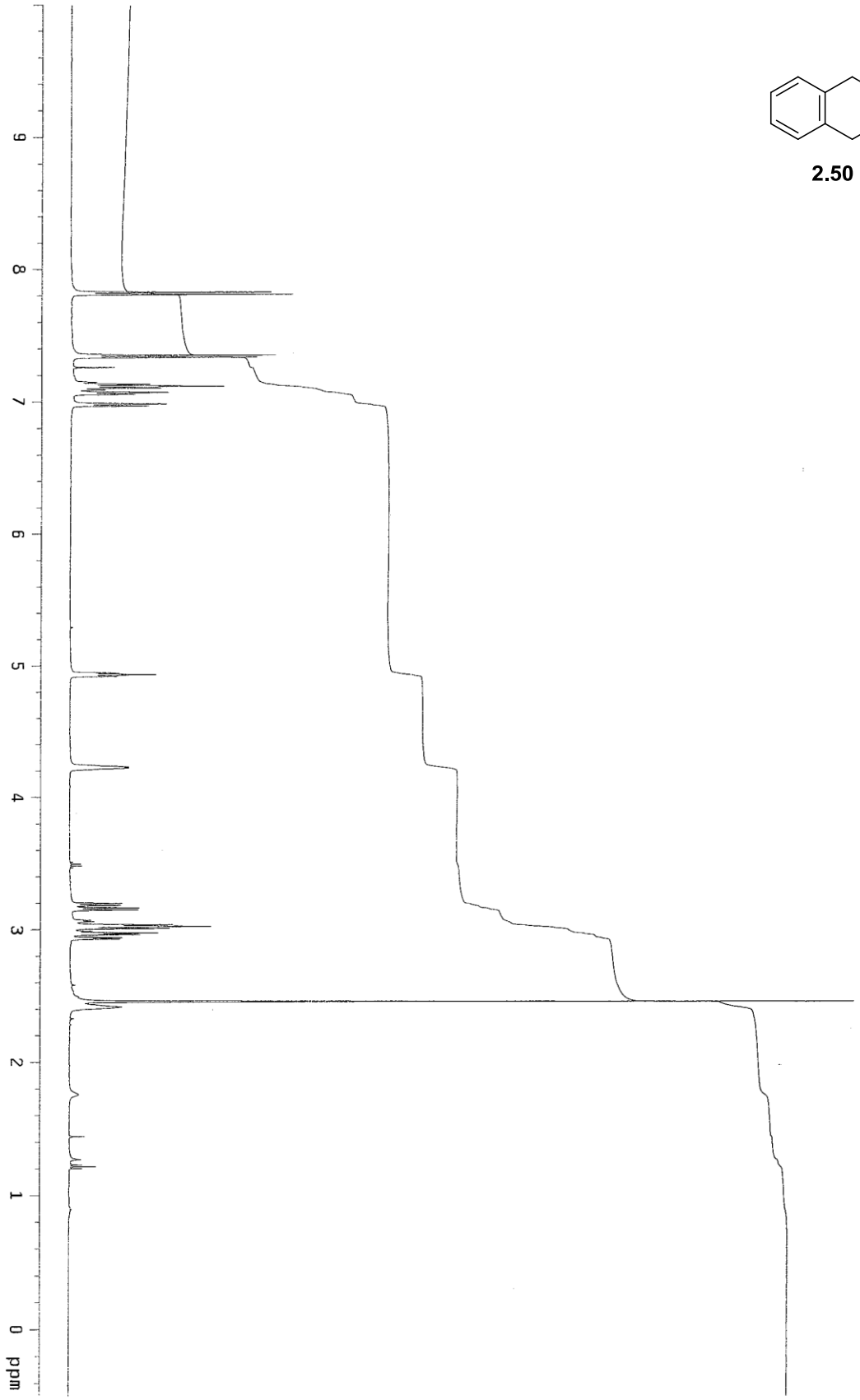
OTs
OH

2.47

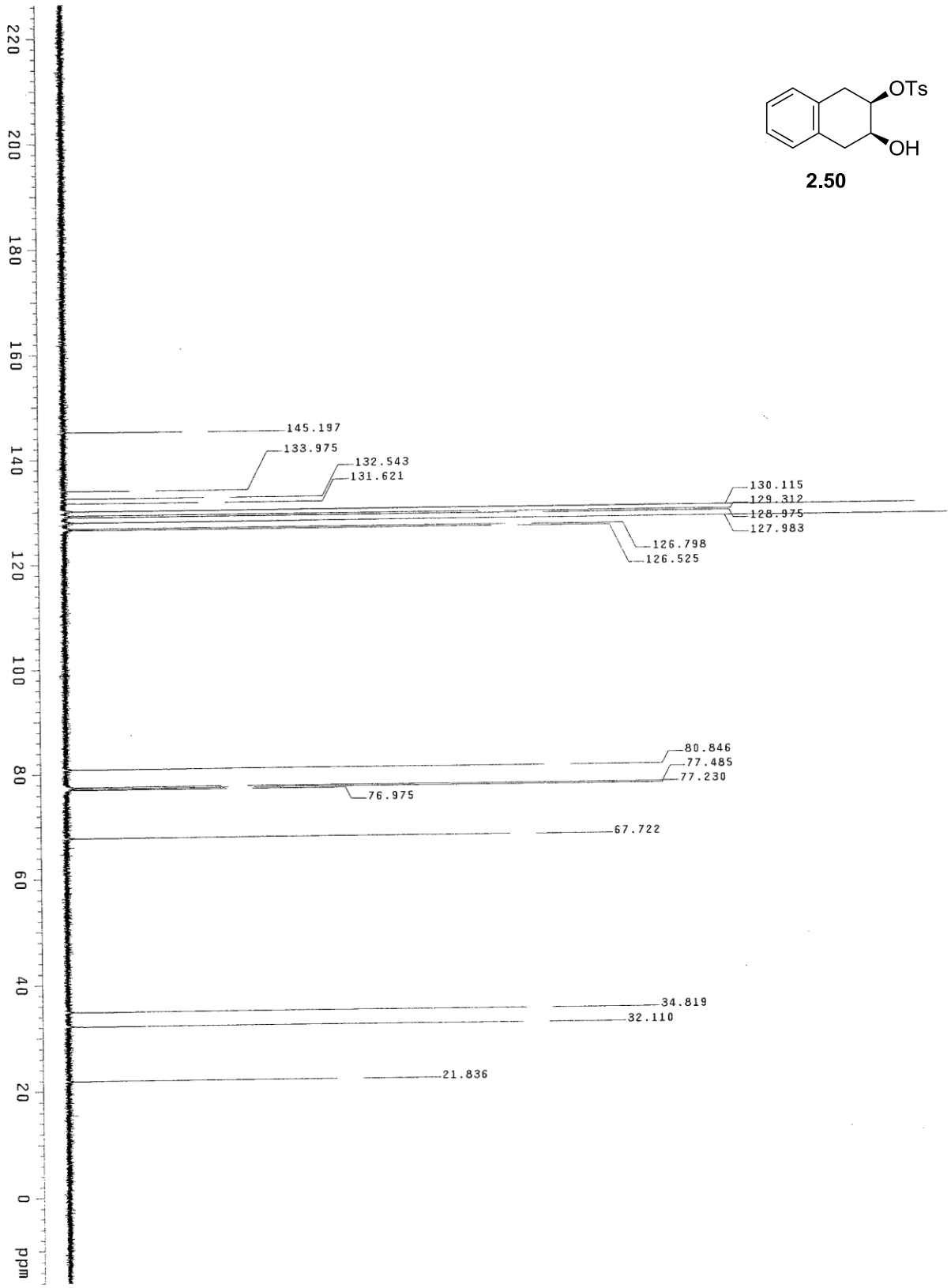

OTs
OH
2.48
9
8
7
6
5
4
3
2
1
0
ppm

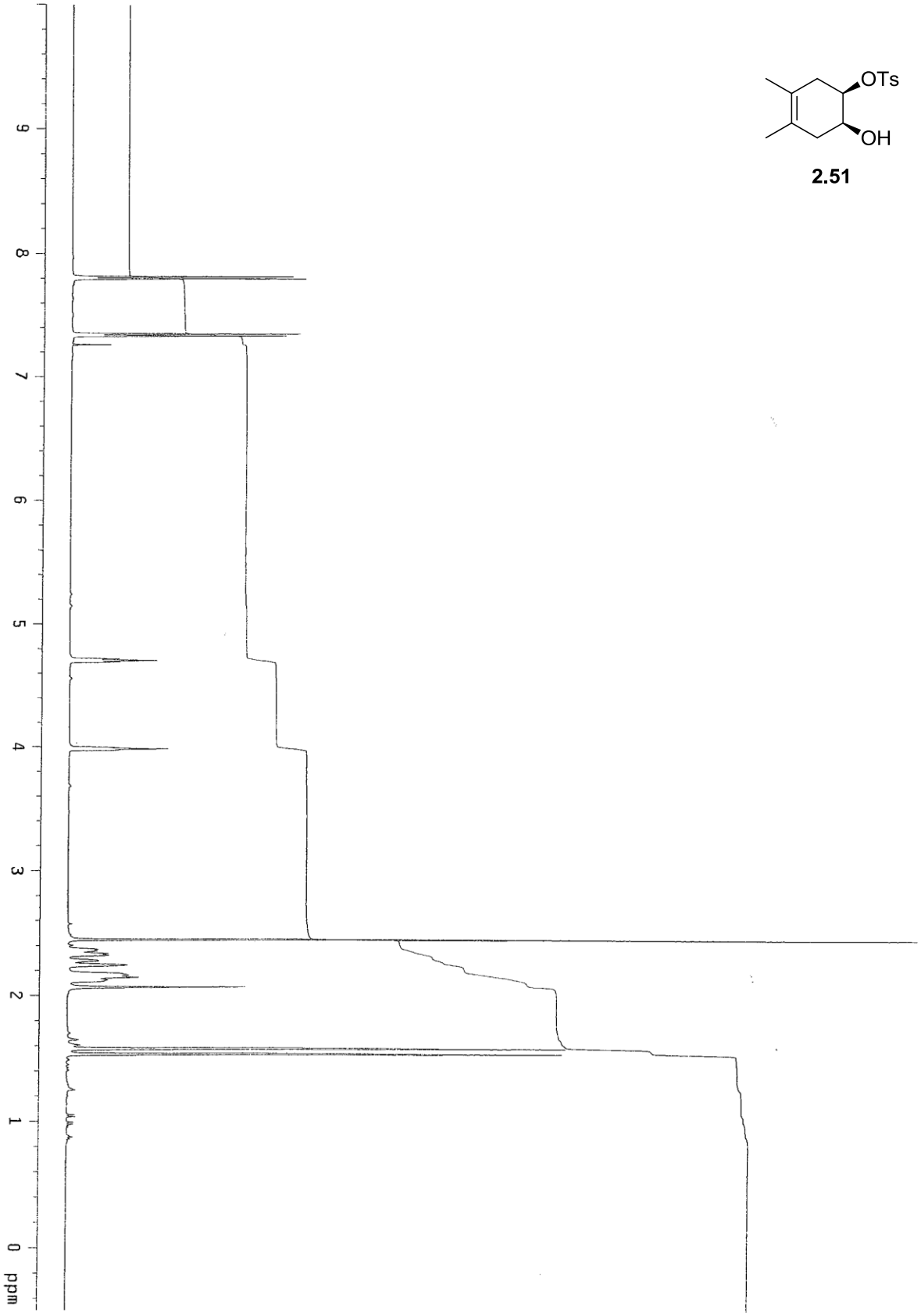

OTs
OH
144.992
133.862
130.791
130.021
129.273
127.941
87.875
77.549
77.230
76.915
73.545
33.239
30.784
21.874
21.809
21.350
200
180
160
140
120
100
80
60
40
20
0
ppm

2.48



2.50


OTs
OH
2.50
145.197
133.975
132.543
131.621
130.115
129.312
128.975
127.983
126.798
126.525
80.846
77.485
77.230
76.975
67.722
34.819
32.110
21.836
220
200
180
160
140
120
100
80
60
40
20
0
ppm



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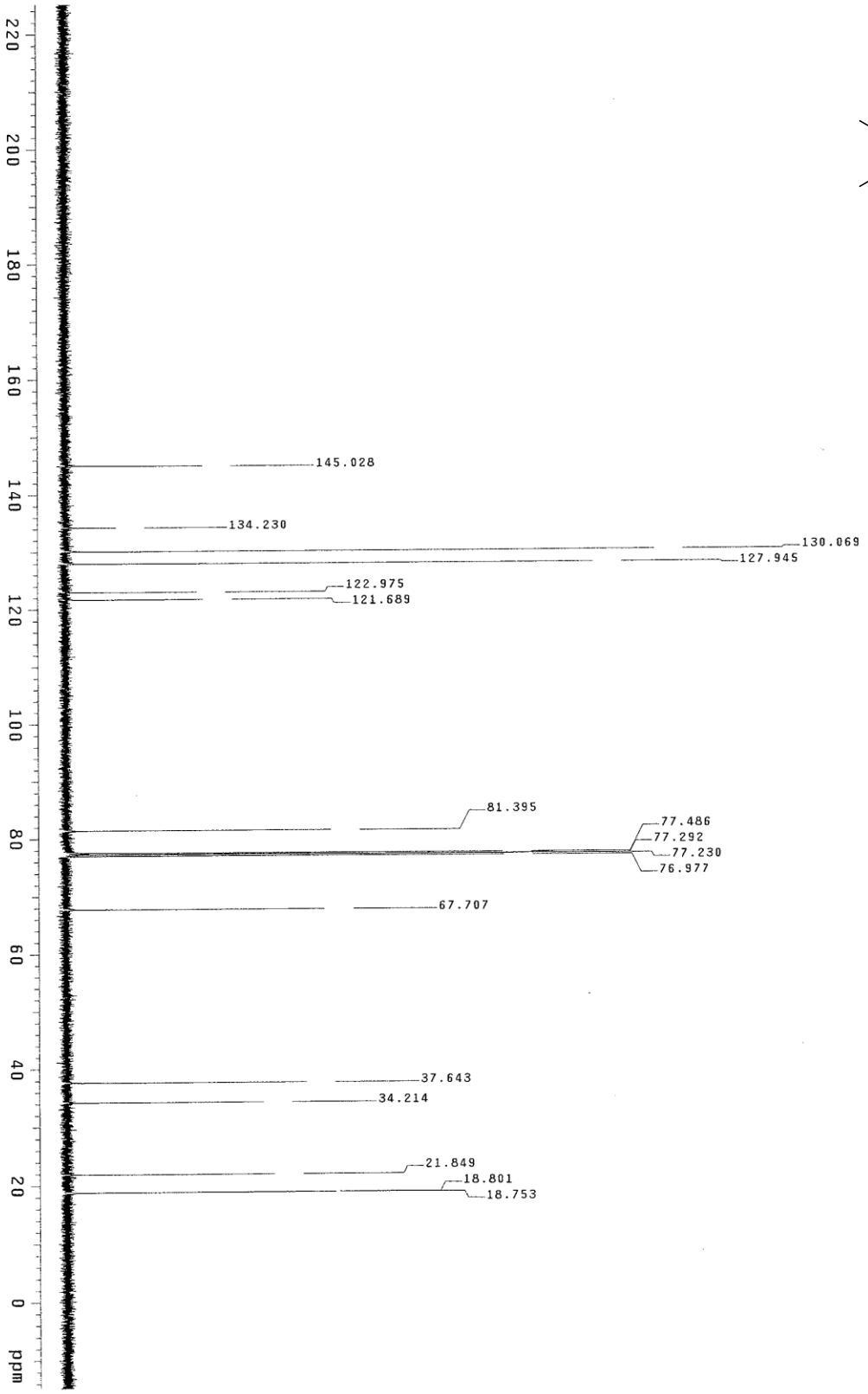
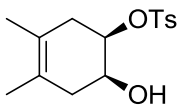
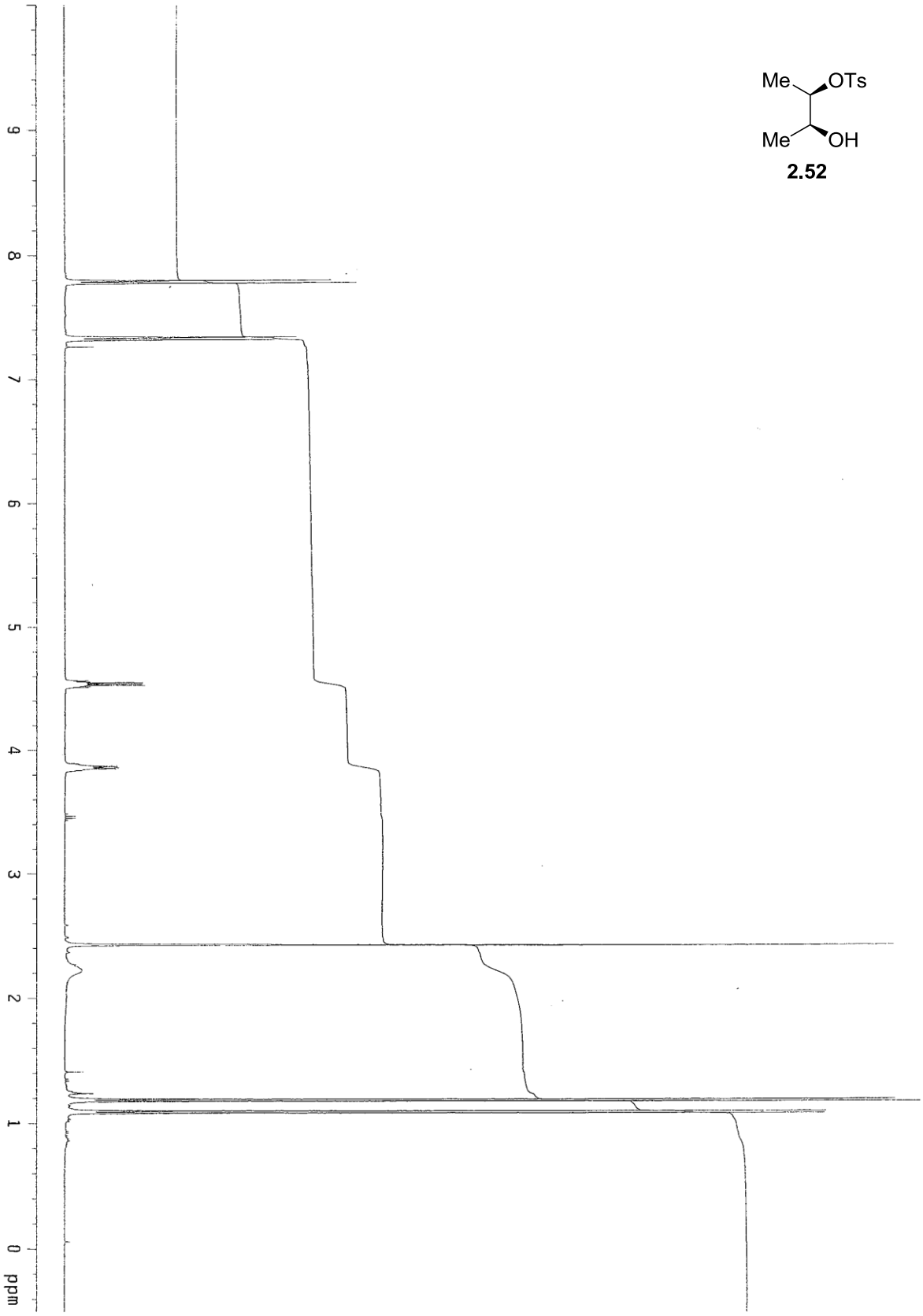
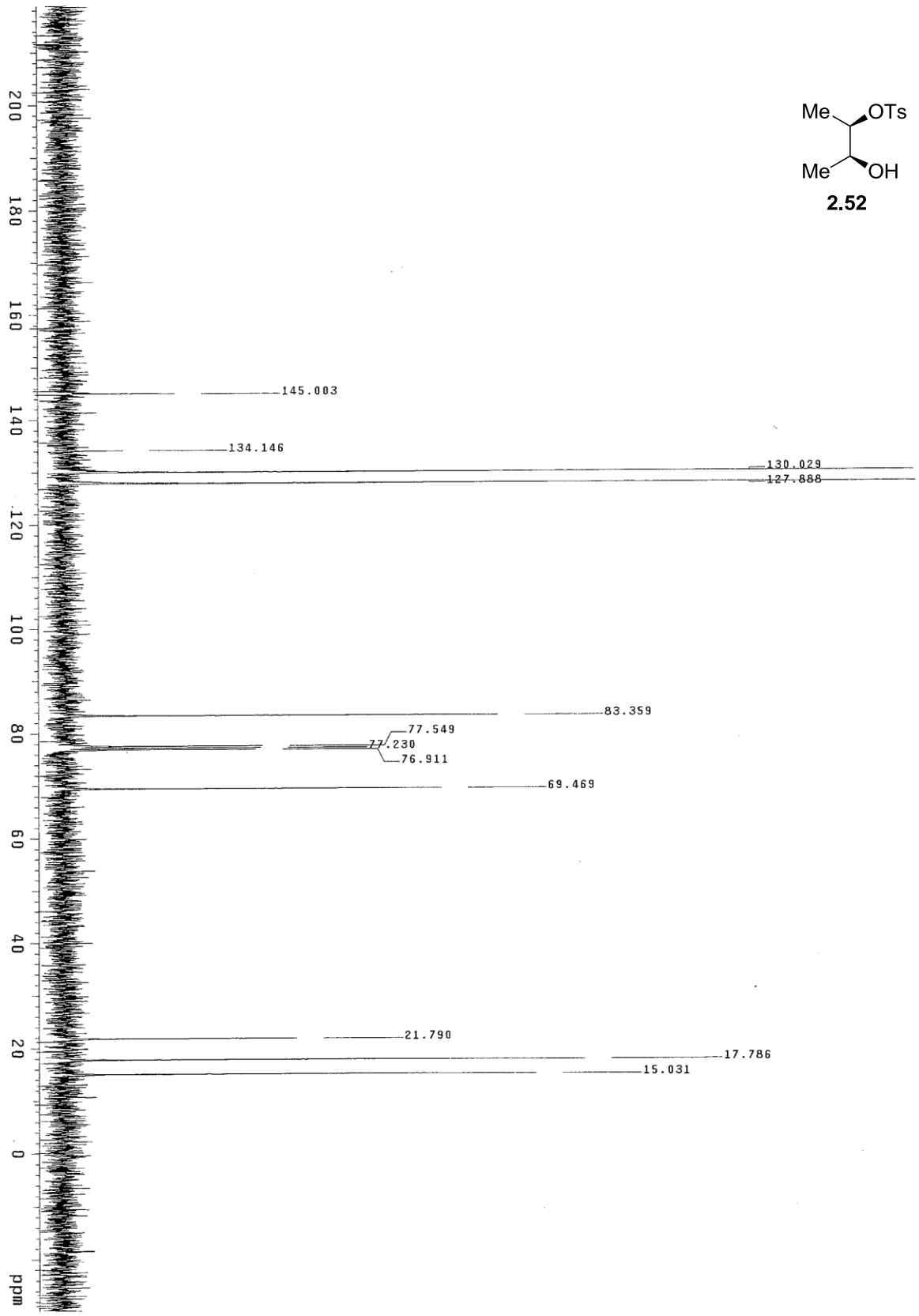
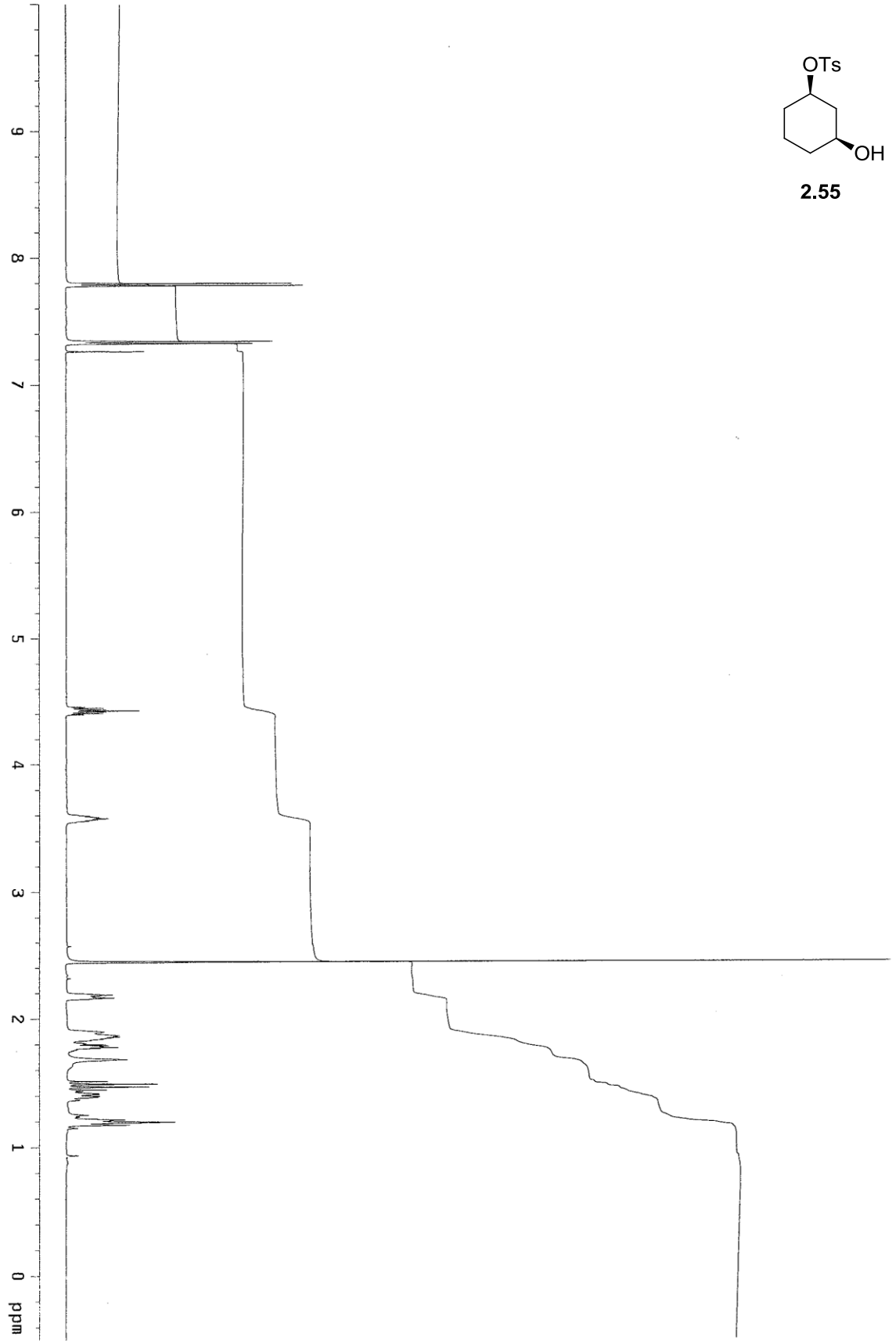

220
200
180
160
140
120
100
80
60
40
20
0
ppm
145.028
134.230
130.069
127.945
122.975
121.689
81.395
77.486
77.292
77.230
76.977
67.707
37.643
34.214
21.849
18.801
18.753

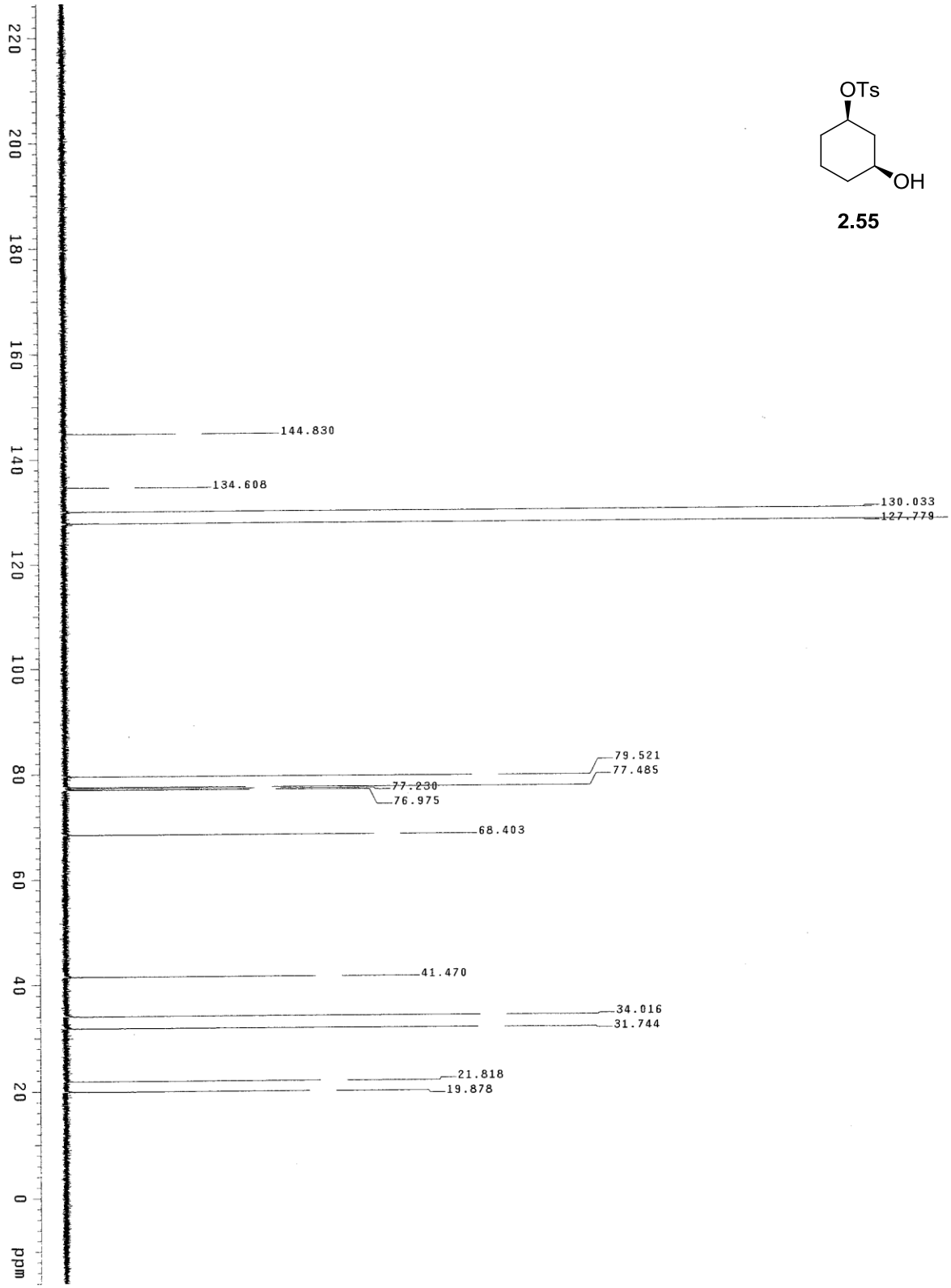

OTs
OH

2.51


Me
OTs
Me
OH
2.52
9
8
7
6
5
4
3
2
1
0
ppm


Me
OTs
Me
OH
2.52
145.003
134.146
130.029
127.888
83.359
77.549
77.230
76.911
69.469
21.790
17.786
15.031
200
180
160
140
120
100
80
60
40
20
0
ppm


OTs
OH
2.55
9
8
7
6
5
4
3
2
1
0
ppm


OTs
OH
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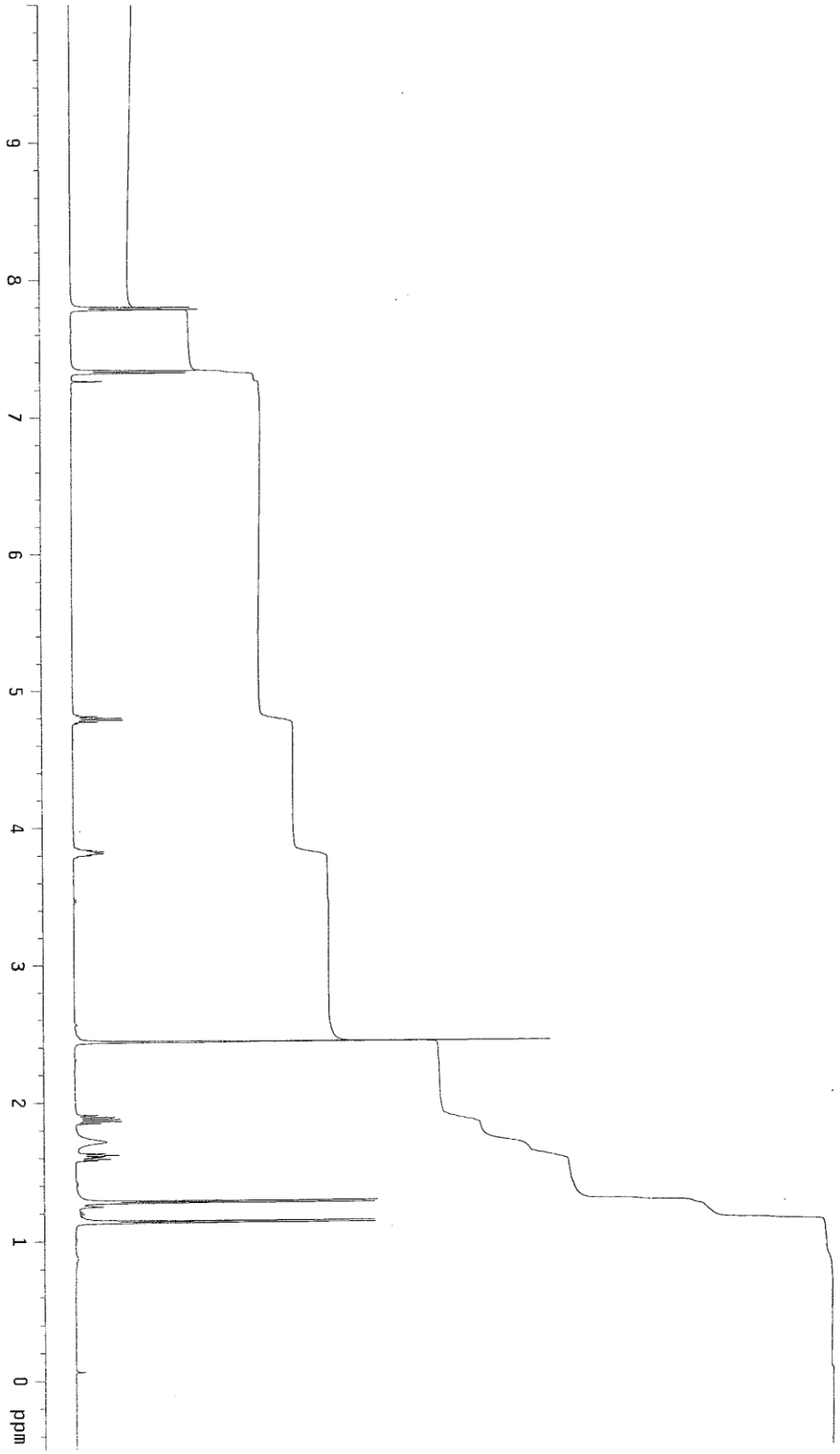
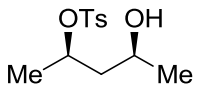
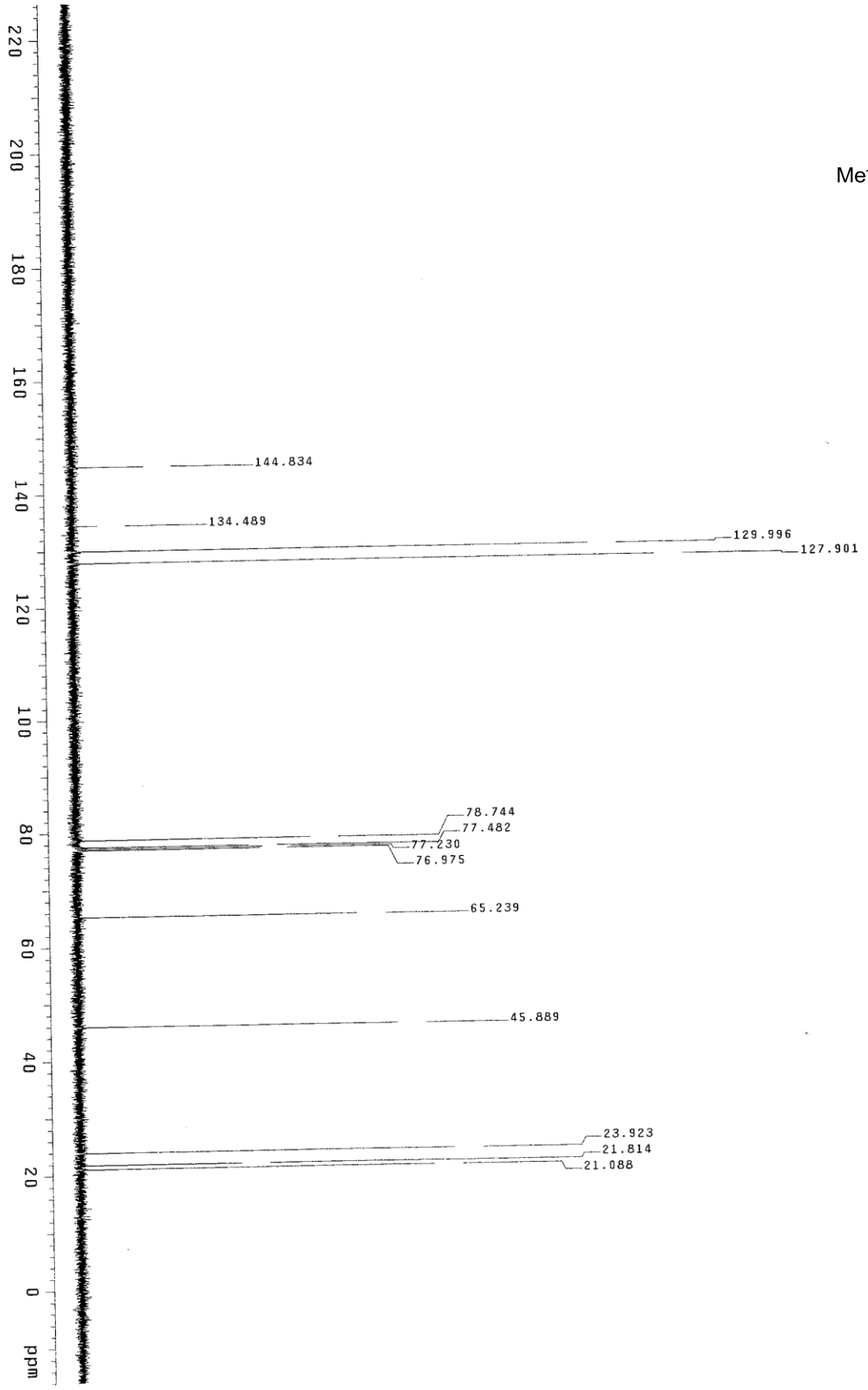
134.608
130.033
127.779
79.521
77.485
77.230
76.975
68.403
41.470
34.016
31.744
21.818
19.878
220
200
180
160
140
120
100
80
60
40
20
0
ppm





2.57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127.901
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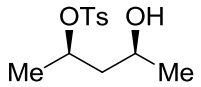
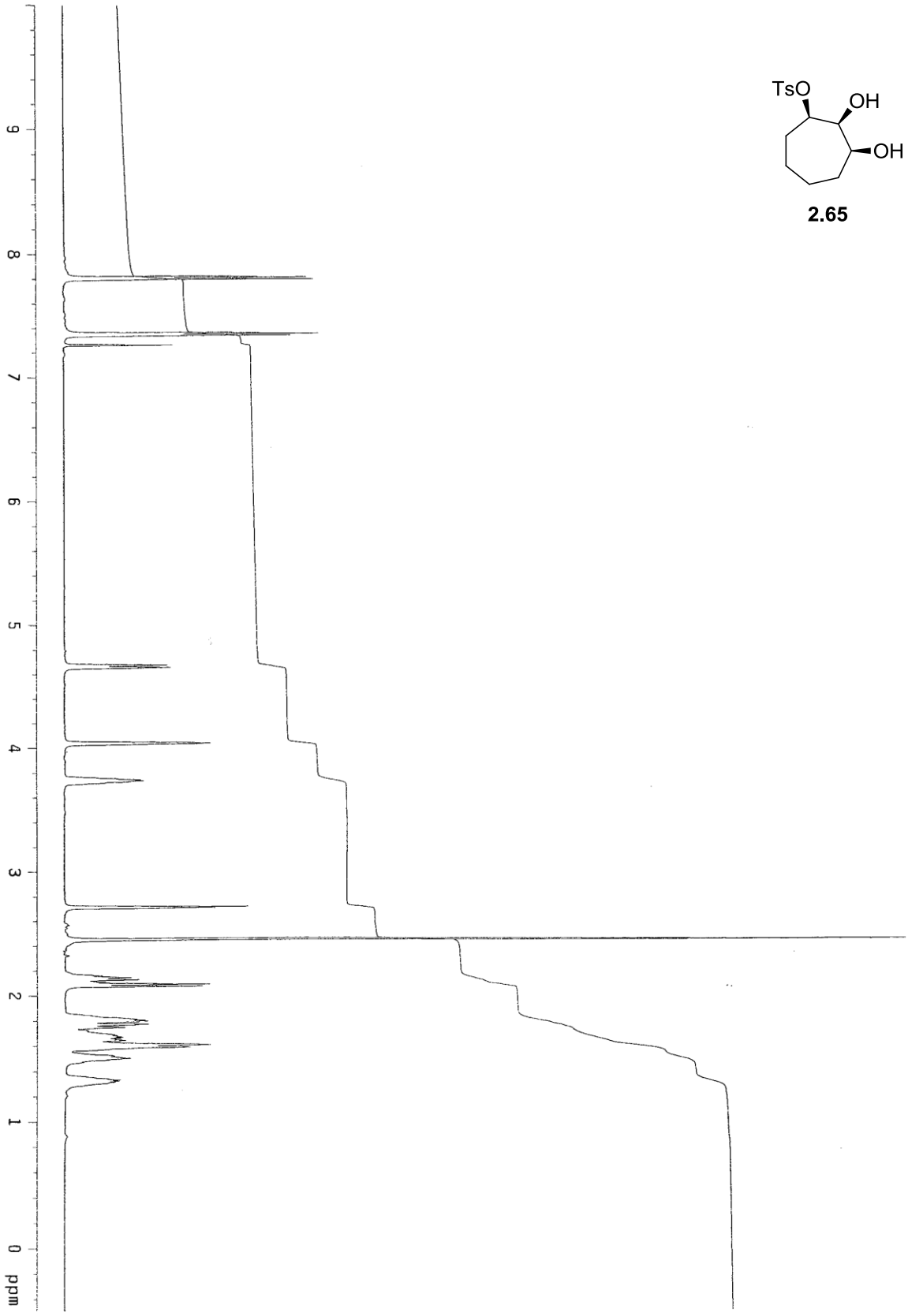
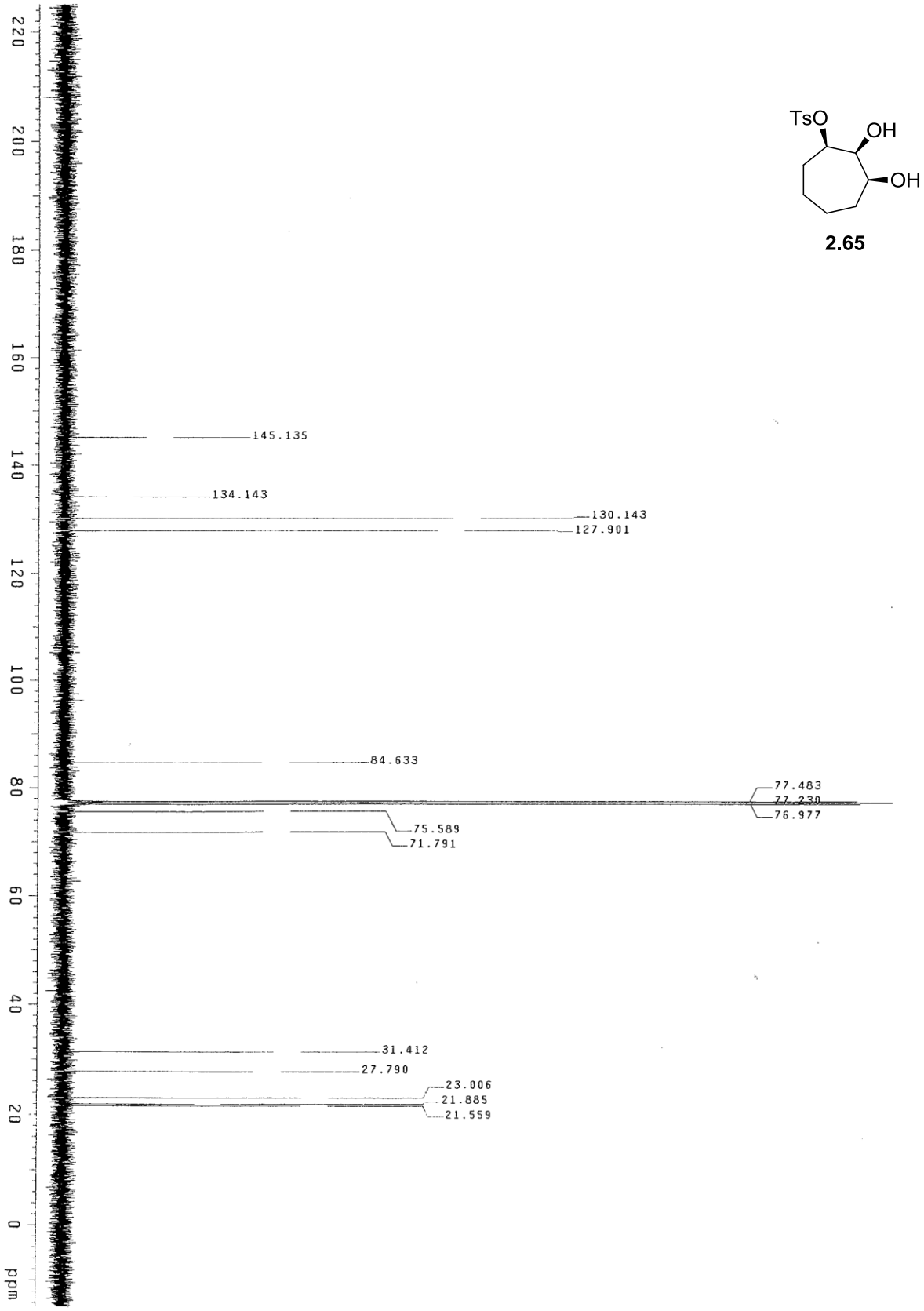
77.482
77.230
76.975
65.239
45.889
23.923
21.814
21.088
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OTs
OH
Me
Me

2.57


TsO
OH
OH
2.65
9
8
7
6
5
4
3
2
1
0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm
145.135
134.143
130.143
127.901
84.633
77.483
77.230
76.977
75.589
71.791
31.412
27.790
23.006
21.885
21.559

TsO
OH
OH

2.65